REMARKS

Applicants thank the Office for the attention accorded the present Application in the March 11, 2005, Office Action. In that Action, Claims 1-10 and 17-18 were rejected under 35 USC §103(a) as being unpatentable over Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. in view of Rork et al.

The Office admits that the references Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. do not expressly teach the incorporation of beta-blockers such as timolol, metoprolol, atenolol, and propranolol, and HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single dosage unit.

The Office cites Rork et al. for the proposition that Rork et al. teaches a sustained release system that can include beta-blockers such as timolol, metoprolol, atenolol, and propranolol and statin cholesterol lowering agents such as simvastatin, pravastatin, and lovastatin. The Office then concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate beta-blockers such as timolol, metoprolol, atenolol, and propranolol with HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single once-a-day dosage unit.

The Office relies on Rork et al. and the knowledge of one of ordinary skill in the art to establish a prima facie case of obviousness, and then responds to Applicants' previous arguments and prior numerous submissions of secondary evidence of

nonobviousness by stating that the arguments are not found persuasive.

The Office further continues to rely *In re Kerkhoven* to state that evidence is required to overcome the prima facie obviousness rejection. Applicants respectfully traverse.

Applicants hereby incorporate their previous arguments as to the applicability of *In re Kerkhoven*.

Applicants remind the Office of the primary purpose of Applicants' invention is to increase compliance with taking medications, especially when multiple medications are required, and to simplify compliance. Applicants further state in Applicants' specification that patients with cardiovascular disease take multiple medications and that the problems with achieving compliance include the inconvenience and confusion with taking multiple medications. (See page 4, lines 16-21). Applicants' invention is provided to increase compliance among patients required to take a beta-blocker and a cholesterol-reducing agent.

Applicants submit new evidence in supporting Applicants' arguments that the combination of a beta-blocker and a cholesterol-lowering medication in a single oral formulation to increase compliance is not obvious. Exhibit 1105-1, submitted herewith, is a copy of a study/investigation by D. F. Blackburn et al. entitled "Adherence to statins, beta-blockers and angiotensin-converting enzyme inhibitors following a first cardiovascular event: a retrospective cohort study", Canadian Journal of Cardiology, Vol. 21, No. 6, May 1, 2005, pages 485-8. The purpose of the study was to report long-

term adherence rates for statins, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors in patients. Adherence was assessed for 1,221 eligible patients from the first statin prescription to a subsequent cardiovascular event.

According to the report, patient adherence to statin medications dropped to 60.3% at one year and 48.8% at five years. The report also indicated that the decline in the proportion of adherent patients was most notable during the first two years (100% to 53.7%). Based on the data from the study, the report concludes that patients who exhibit optimal adherence (i.e. compliance) over one to two years after their initial cardiovascular event generally remain adherent over subsequent years and that adherence to beta-blockers and ACE inhibitors is significantly associated with statin adherence in a subset of patients. However, this publication also reports that adherence was negatively influenced if statin medications were prescribed after the initiation of beta-blockers or ACE inhibitors. (See column 1, page 487, last paragraph under RESULTS).

This report is evidence that compliance to multiple medications is influenced by the type of medication (statins, beta-blockers, ACE inhibitors) prescribed and when one type of medication (statin) is prescribed relative to other medications (beta-blockers, ACE inhibitors). This further supports Applicants' contention that the present invention will improve compliance since prescribing the statin in the single dosage unit of the present invention would alleviate the negative influence associated with prescribing the statin after the initiation of the beta-blocker.

In further support of Applicants' contention that simplifying the dosage of multiple medications is likely to increase compliance especially in older patients, Applicants' submit Exhibit 1105-2, which is a copy of an article authored by Frank Lefevre, M.D. et al., titled "Special Report: Interventions to Improve Patient Adherence with Medications for Chronic Cardiovascular Disorders," Tec Assessment Program, Vol. 18, No. 12, November 2003. The objective of the report was to review the evidence on the effectiveness of interventions to improve patient adherence with prescribed cardiovascular medications. The report concluded that there is evidence that a variety of interventions can be effective in improving adherence but that **there is consistent and robust evidence that simplifying medication dosage schedules leads to improved adherence**.

Applicants' claimed invention is a simplification of medication dosage and dosage schedules, i.e. simplifying medication to improve compliance. Exhibit 1105-2 is evidence that supports Applicants' arguments that improvement in compliance involves many factors but that simplifying medication dosage schedules leads to improved adherence (i.e. compliance).

Applicants further submit Exahibit 1105-3, which is a copy of an article authored by Li Wei et al. titled "Use and adherence to beta-blockers for secondary prevention of myocardial infarction: who is not getting the treatment?," Pharmacoepidemiology and Drug Safety, Vol. 13, pp. 761-766, April 23, 2004. The purpose of this study was to characterize those who receive beta-blocker therapy after myocardial infarction (MI)

and to estimate the effect of adherence to beta-blocker use on subsequent mortality and recurrent MI. The study stated that non-adherence or poor adherence to drug treatment is a significant problem in the management of chronic disease. A community-based observational cohort study was done using a record linkage database from which a total of 865 patients were included in the study. The study concluded that beta-blocker use was lower in older patients but that these patients appeared to have the greatest benefit.

This study supports Applicants' contention that the group for which a small improvement in compliance would reap the greatest benefits is the group represented by older patients. These are patients identified in Applicants' disclosure as the group most likely to have compliance problems because the older patients with cardiovascular problems are known to commonly utilize many medications.

Applicants further submit Exhibit 1105-4, which is a copy of an article authored by Julia Hippisley-Cox et al. titled "Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis," British Medical Journal, Vol. 330, pp. 1059-1063, May 7, 2005. The purpose of the study was to determined the effect of combinations of statins, aspirin, beta-blockers, and ACE inhibitors in the secondary prevention of all cause mortality in patients with ischaemic heart disease. The study is significant for disclosing what was already known on the topic and for what the study added. It was known that statins are associated with improved survival in patients with ischaemic heart disease but that direct evidence was

lacking for the effects of combinations of drugs in cardiovascular disease.

The study included 13,029 patients who had a first diagnosis of ischaemic heart disease. 2,226 cases were matched to 9,064 controls. The study reported that the treatments associated with the smallest reduction in all cause mortality were beta-blockers alone with a 19% reduction, ACE inhibitors alone with a 20% reduction, combined statins and ACE inhibitors with a 31% reduction, and statins alone with a 47% reduction.

The study further reported that the drugs associated with the greatest reductions in odds for all cause mortality were combinations of statins, aspirin and beta-blockers with an 83% reduction; statins, aspirin, ACE inhibitors, and beta-blockers with a 75% reduction; and statins, ACE inhibitors and aspirin with a 71% reduction.

The study is also noteworthy for the reduction in odds for all cause mortality for the combination of statins and beta-blockers with a 54% reduction. (See Table 2, Adjusted Odds Ratio).

The study concluded that combinations of statins, aspirin and beta-blockers improves the survival in high risk patients with cardiovascular disease but that the addition of an ACE inhibitor conferred no additional benefit.

This study is significant for two reasons.

First, it refutes the Office's contention that combining one agent such as an ACE inhibitor (an agent the Office considers "useful to reduce risk of cardiovascular disease individually") with other such agents similarly categorized by the Office would be

beneficial. The study shows that the addition of an ACE inhibitor conferred no additional benefit. Moreover, the combination would only subject the patient to the potential for side effects of ACE inhibitors. These side effects (according to Captopril Tablets, PDR 2005, pp. 2217-2220) include anaphylactoid reactions, angioedema, cough, renal insufficiency, hypotension, and vasculitis.

Combining agents that the Office considers "useful for a similar purpose" is medically unsubstantiated and, because of the potential for detriment, the report teaches against the Office's assertion that it is obvious to combine such agents into a single dosage unit. This report further speaks to the differences in modes of action, interaction, and nuances between medicinal agents and the consequences of faulty and overly broad categorization applied by the Office.

Second, it provides evidence of unexpected results showing that the combinations of drugs on all cause mortality in patients with ischaemic heart disease provided increased benefits over those of each drug individually, which was heretofore unknown. For example, statins alone provided a 47% reduction in odds for all cause mortality and beta-blockers alone provided a paltry 19% reduction. Yet, the combination of statins and beta-blockers provided a 54% reduction in odds for all cause mortality in patients with ischaemic heart disease. The reduction in odds for all cause mortality in patients with ischaemic heart disease is greater for Applicants' combination of statins and beta-blockers than for either medication alone.

In summary, the secondary evidence provided by Exhibits 1105-1 to 1105-4

shows the unexpected benefits of Applicants' invention. The combination of statins and beta-blockers in a single dosage unit provides a simplified medication regimen (which has been shown to increase compliance especially in older patients taking multiple medications), averts the negative influence on compliance when statin medications are prescribed after the initiation of beta-blockers, and provides a reduction in odds for all cause mortality in patients with ischaemic heart disease over each medication alone.

Conclusion

It is clear that, when Applicants' invention is viewed as a whole, the prior art contains no suggestion to combine Applicants' cardiovascular treatment medications into a single dosage unit.. Where Applicants' components are similar to those components shown and disclosed in the prior art, the law requires that the prior art also contain some teaching, suggestion or incentive for arriving at Applicants' claimed structure. The Office has failed to provide this showing. On the other hand, Applicants have provided evidence of noncompliance problems, the under-utilization of medications, and the unexpected reduction in odds for combinations of cardiovascular medications for all cause mortality in patients with ischaemic heart disease, and confirmation that non-adherence or poor adherence to drug treatment is still a significant problem in the management of chronic diseases.

In light of the above arguments, Applicants respectfully submit that Claims 1-10 and 17-18 of the present application contain allowable subject matter and that the 35

USC §103(a) rejections have been successfully traversed.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,

Dated: 11/17/05

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I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office, Fax No. (571) 273-8300 on November 17, 2005.

Robert R Deleault

Exhibit 1105-1

Adherence to statins, beta-blockers and angiotensin-converting enzyme inhibitors following a first cardiovascular event: A retrospective cohort study

David F Blackburn PharmD[1], Roy T Dobson PhD[1], James L Blackburn PharmD[1], Thomas W Wilson MD FRCPC[2], Mary Rose Stang PhD[3], William M Semchuk PharmD[1,4]

DF Blackburn, RT Dobson, JL Blackburn, TW Wilson, MR Stang, WM Semchuk. Adherence to statins, beta-blockers and angiotensin-converting enzyme inhibitors following a first cardiovascular event: A retrospective cohort study. Can J Cardiol 2005;21(6):485-488.

BACKGROUND: Population studies of statin adherence are generally restricted to one to two years of follow-up and do not analyse adherence to other drugs.

OBJECTIVES: To report long-term adherence rates for statins, angiotensin-converting enzyme (ACE) inhibitors and beta-blockers in patients who recently experienced a first cardiovascular event.

METHODS: Linked administrative databases in the province of Saskatchewan were used in this retrospective cohort study. Eligible patients received a new statin prescription within one year of their first cardiovascular event between 1994 and 2001. Adherence to statins, beta-blockers and ACE inhibitors was assessed from the first statin prescription to a subsequent cardiovascular event.

RESULTS: Of 1221 eligible patients, the proportion of patients adherent to statin medications dropped to 60.3% at one year and 48.8% at five years. The decline in the proportion of adherent patients was most notable during the first two years (100% to 53.7%). Several factors were associated with statin adherence, including age (P=0.012), number of physician service days (P=0.037), chronic disease score (P=0.032), beta-blocker adherence (P<0.001) and ACE inhibitor adherence (P<0.001). Adherence to beta-blockers and ACE inhibitors was very similar to adherence to statin medications at each year of follow-up.

CONCLUSIONS: Patients who exhibit optimal adherence over one to two years after their initial cardiovascular event generally remain adherent over subsequent years. Also, adherence to beta-blockers and ACE inhibitors is significantly associated with statin adherence in a subset of patients; however, overall adherence to all three drugs was similarly poor.

Key Words: *ACE inhibitors; Beta-blockers; Compliance; Statins*

L'observance des statines, des bêta-bloquants et des inhibiteurs de l'enzyme de conversion de l'angiotensine après un premier événement cardiovasculaire : Une étude rétrospective de cohortes

HISTORIQUE : En général, les études de l'observance des statines par la population sont limitées à la première année ou aux deux premières années de suivi et n'analysent pas l'observance d'autres médicaments.

OBJECTIFS : Rendre compte des taux d'observance des statines, des inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) et des bêta-bloquants chez des patients ayant récemment vécu un événement cardiovasculaire.

MÉTHODOLOGIE : Des bases de données administratives reliées de la province de la Saskatchewan ont été utilisées dans cette étude rétrospective de cohortes. Les patients admissibles ont reçu une nouvelle prescription de statines dans l'année suivant leur premier événement cardiovasculaire, entre 1994 et 2001. L'observance des statines, des bêta-bloquants et des IECA a été évaluée entre la première prescription de statines et un événement cardiovasculaire subséquent.

RÉSULTATS : Sur les 1 221 patients admissibles, la proportion qui avait respecté sa prescription de statines a chuté à 60,3 % au bout d'un an et à 48,8 % au bout de cinq ans. Le fléchissement de la proportion de patients qui respectaient le traitement était le plus marqué pendant les deux premières années (100 % à 53,7 %). Plusieurs facteurs s'associaient à l'observance des statines, y compris l'âge (P=0,012), le nombre de jours de service des médecins (P=0,037), l'indice de maladie chronique (P=0,032), l'observance des bêta-bloquants (P<0,001) et l'observance des IECA (P<0,001). L'observance des bêta-bloquants et des IECA était très similaire à celle des statines à chaque année de suivi.

CONCLUSIONS : Les patients qui affichent une observance optimale pendant un ou deux ans après leur premier événement cardiovasculaire maintiennent généralement ce cap par la suite. De plus, l'observance des bêta-bloquants et des IECA est considérablement associée à celle des statines dans un sous-groupe de patients. Toutefois, l'observance globale aux trois médicaments était tout aussi faible.

In contrast to the adherence rates reported in secondary prevention trials (1-3), observational studies (4-10) suggest that statin adherence falls dramatically over one to two years from the first statin prescription. However, information about adherence beyond two years is limited (6,9). In many studies (5-8,10), the adherence exhibited by patients with cardiovascular diseases seems to be higher than that of patients at low risk, but it is not known whether there are differences in adherence among patients with different types of cardiovascular disease or those with single versus multiple previous events. Also, adherence to concomitant medications, such as beta-blockers and angiotensin-converting enzyme (ACE) inhibitors, has not been frequently examined and, thus, it is unknown whether nonadherence is more problematic with statins than with other mortality-reducing agents.

The purpose of the present study was to report long-term adherence to statin medications in patients who had experienced a first cardiovascular event. In addition, we determined

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TABLE 1
Percentage of patients adherent to statin medications using two types of adherence measures*

	Year (number of patients)				
Adherence measure	1 (1140)	2 (840)	3 (591)	4 (395)	5 (207)
Number of tablets/day† (%)	60.3	52.6	51.1	49.1	47.8
Fill frequency‡ (%)	61.8	53.7	53.5	49.6	48.8

*In an attempt to validate the adherence measure, adherence rates were calculated and compared using two distinct equations: fills/month (fill frequency) and tablets/day. These two measures were very highly correlated (r=0.95; P<0.001) and virtually identical at every year of follow-up among statin users; †Data from reference 9; ‡Number of prescription fills divided by number of months (34 days) of observation

adherence rates to beta-blockers and ACE inhibitors in this population of statin users.

METHODS

Linked administrative data of patients receiving a new statin prescription after experiencing their first cardiovascular event between January 1, 1994, and December 31, 2001, were used in this retrospective cohort study. A statin prescription was considered new if there were no statin prescriptions documented in the previous five years. The initial cardiovascular event could be a myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty or coronary artery bypass graft. All initial events were identified by primary discharge diagnoses (*International Classification of Diseases, 9th Revision* [11] coded), procedures in the hospital services database or service codes in the physician services database.

Patient adherence was evaluated from the first statin prescription until a recurrent cardiovascular event (myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft or stroke), death, diagnosis of HIV, solid organ transplantation, coverage termination (eg, leaving the province) or the end of the observation period (ie, December 31, 2001). Also, patients were excluded if a recurrent cardiovascular event occurred within 10 months of the first prescription (n=18). These exit criteria were developed for a separate analysis intended to accurately identify cardiovascular events resulting from nonadherence to statin medications. The present paper reports the long-term adherence to statins, beta-blockers and ACE inhibitors in patients following their first cardiovascular event.

All study data were provided from linked administrative databases in the province of Saskatchewan. The Government of Saskatchewan maintains several databases of information regarding health services use, including prescription drug data, hospital services data, physician services data and vital statistics information (12). These administrative databases have been electronically linked to provide data for several observational studies (13-15). For the present analysis, drug data were obtained from the Prescription Drug Plan database. Over 90% of the population of Saskatchewan is eligible for drug plan benefits and all Saskatchewan pharmacies are equipped with point-of-service terminals connected to the database. Information transmitted to the database on each prescription fill includes the date, drug name, brand name, quantity dispensed and patient information. All patients were de-identified and given a unique random number for the purpose of linking information only.

Adherence analysis

In Saskatchewan, most cardiovascular medications, including statins, beta-blockers and ACE inhibitors, are dispensed in one-month

TABLE 2
Baseline characteristics of patients

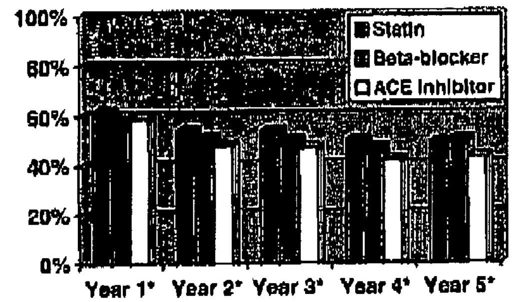
Characteristic	Adherence ≥80% (n=661)	Adherence <80% (n=560)
Male (%)	76.6	77.5
Mean age at index event (years) (SD)	58.6 (8.7)	57.4 (9.0)
Index event (%)		
Myocardial infarction	43.0	39.0
Unstable angina	14.0	16.8
PTCA	38.3	40.4
CABG	4.7	4.1
Patients with ≥1.5 physician service days per month (%)	17.5	12.7
Mean physician service days per month (SD)	1.08 (0.75)	0.93 (0.65)
Mean chronic disease score (SD)*	8.4 (2.9)	8.1 (3.0)
Diabetes (%)	28.1	24.3
ACE inhibitor use (at least one fill) (%)	54.5	42.9
Beta-blocker use (at least one fill) (%)	70.3	62.3
Mean follow-up (years) (SD)	3.0 (1.7)	3.3 (1.7)

*Chronic disease score was calculated on the basis of medication use (13,17). ACE Angiotensin-converting enzyme; CABG Coronary artery bypass graft; PTCA Percutaneous transluminal coronary angioplasty

(34 day) quantities. Therefore, adherence to these medications was measured using the fill frequency, calculated by dividing the number of prescription fills during the observation period by the number of months of observation. For example, a patient filling eight prescriptions during a 10-month period (340 days) would be considered 80% adherent. The authors found a very high correlation (r=0.95; P<0.001) between the fill frequency and another measure used to determine statin adherence (9) (ie, number of statin tablets dispensed divided by number of days of observation) (Table 1). Patients were allowed to switch between agents within the same class without affecting their adherence status. Similar to patients in other studies (5,6,9,16), patients in the present study were considered adherent if they exhibited rates of 80% or greater.

For each of the five years following the initial statin prescription, the proportion of patients who remained adherent (80% or greater) to statins, beta-blockers and ACE inhibitors was determined. However, many subjects had not filled a prescription for a beta-blocker or an ACE inhibitor because the study's eligibility criteria required only an initial statin prescription. Therefore, the proportion of patients adherent to statin medications was determined from the entire population, but the proportions adherent to beta-blockers and ACE inhibitors were restricted to those receiving at least one prescription for a beta-blocker or an ACE inhibitor during the observation period. In this way, the proportion of adherent patients was consistently based on patients receiving at least one prescription for the agent of interest.

Linear regression analysis using fill frequency to statin medications as the dependent variable was performed on the entire population of statin users. Several covariates were entered into the model, including sex, age on day of first statin prescription, initial statin prescribed, presence of diabetes (hospital diagnosis, or prescription for insulin or an oral hypoglycemic), and days hospitalized and 'physician service days' per month of observation. Physician service days were estimated by the number of distinct dates in which physicians' fees for service claims, including outpatient visits, were submitted to the physician services database.



*Number of eligible patients at each interval

	Year 1	Year 2	Year 3	Year 4	Year 5
Statin users	1140	840	591	395	207
Beta-blocker users	707	525	365	237	116
ACE inhibitor users	435	313	214	147	77

Figure 1) *Percentage of patients adherent to statins, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors. Adherence was calculated using the number of patients filling at least one prescription for each respective medication as the denominator*

Additional covariates included time to first prescription from initial cardiovascular event, type of event, survival time, chronic disease score based on overall medication use (17), ACE inhibitor adherence, beta-blocker adherence, prior use of beta-blockers or ACE inhibitors, and period of entry into the study (1994 to 1996, 1997 to 1998 or 1999 to 2001). All analyses were performed using SPSS for Windows version 12.0 (SPSS Inc, USA).

RESULTS

One thousand two hundred twenty-one subjects filled a new statin prescription within a year of their first cardiovascular event (Table 2). The mean age of patients was 58 years, 77% were men and 26.4% had diabetes. The statins initially prescribed were atorvastatin (29.3%), pravastatin (26.1%), simvastatin (25.6%), fluvastatin (8.4%), lovastatin (6.2%) and cerivastatin (4.3%). Among the statin users, 814 patients (66.7%) filled at least one beta-blocker prescription and 600 patients (49.1%) filled at least one ACE inhibitor prescription. Only 34.8% (n=425) of the statin users filled at least one prescription for a beta-blocker and an ACE inhibitor. The average period of observation was longer than three years (mean 38.5±21 months, range 10 months to eight years).

One year after the first statin prescription, 61.6% of subjects remained adherent to statins. This number gradually declined to 48.8% at five years. Of interest, among the subgroups of patients taking beta-blockers or ACE inhibitors, adherence rates to these medications were strikingly similar to those of statins (Figure 1). Although a definite subgroup of patients refilled all three prescriptions regularly, nonadherence to these medications appeared randomly distributed, with no single medication being selectively neglected (data not shown).

Linear regression analysis implicated a number of covariates that were significantly associated with statin adherence, including increasing age (P=0.012), number of physician service days per month (P=0.037), chronic disease score (P=0.032), increasing beta-blocker adherence (P<0.001) and increasing ACE inhibitor adherence (P<0.001). In contrast, adherence was negatively influenced if statin medications were prescribed after the initiation of beta-blockers (P=0.017) or ACE inhibitors (P<0.001).

DISCUSSION

Two years after the initial prescription, 53.7% of our population remained adherent to their statin medication. Although this rate is not optimal, it compares favourably with two-year adherence rates of 32% (6) and 40% (8) in two recently published trials. Others (5,10) have reported even lower adherence rates to statin medications. Compared with the populations in the studies mentioned above (6,8), our population was younger and had recently experienced a first cardiovascular event. Although recent cardiovascular morbidity has been associated with higher adherence (5-8,10), our analysis was limited to patients experiencing their first cardiovascular event, while previous investigators have not made this distinction. We believe patient adherence is likely higher after a first event than after a second or third event, which could explain the higher adherence rates reported in the present study. Further study is needed to clarify the impact of cardiovascular morbidity on statin adherence.

We observed 48.8% of patients to be adherent at five years. Larsen et al (9) observed a 50% adherence rate at three years, while Benner et al (6) found that only 26% of patients remained adherent at five years. However, in the latter report, the inclusion of patients without cardiovascular disease was likely responsible for the extremely low adherence rate. Similar to populations in other studies, our population demonstrated a significant drop in adherence over the first two years but stabilized between year 3 (53.5%) and year 5 (48.8%). The first two years of therapy appear to be a critical period during which follow-up and support of all new statin users should be intensive. However, statin adherence appears to stabilize after two years of therapy.

Previous statin adherence studies have not evaluated concomitant medications, such as ACE inhibitors and beta-blockers. In our sample of statin users, adherence to these medications appeared to be equally poor to that of statins (Figure 1). These data suggest that the commonly reported problem of statin nonadherence may be a signal of overall medication nonadherence because statin nonadherence was not uniquely low in our population.

Similar to other statin adherence studies (6,9,10,18,19), in our study we found that increasing age was associated with statin adherence. However, we also observed significant associations among beta-blocker, ACE inhibitor and statin adherence. In contrast to the notion that higher numbers of daily medications reduce adherence (18), our findings suggest that this may not always be true. Similar findings have been reported recently in patients receiving lipid-lowering or ACE inhibitor therapy (16).

Our analysis had certain limitations. Our inclusion criteria were intended to identify a homogeneous population of new statin users who recently experienced a first cardiovascular event. These criteria identified only a portion of the statin, ACE

inhibitor and beta-blocker users in Saskatchewan. However, it is likely that our results are compatible with those of the entire population of patients taking these drugs. In fact, our study population may have demonstrated higher than average adherence rates because recent cardiovascular morbidity appears to improve adherence (5,8-10). We assumed that filling a statin prescription meant consuming the entire supply. Considering that many patients pay for their statin medications in Saskatchewan, it is unlikely that patients would purchase this expensive medication but not consume the supply. However, we were unable to account for levels of income or co-payment status, which may be a factor influencing medication adherence. Also, we assumed adherent patients must fill one prescription per month. This restriction was relatively conservative because some patients may split doses, allowing every other month filling. However, patients who refilled their prescriptions every month were likely to be correctly identified as adherent. Despite using this conservative measure, we found a relatively high rate of adherence compared with the reported rates in other jurisdictions.

Although we can accurately assess frequency of medication fills from our drug plan database, it is impossible to determine the reasons for nonadherence. Although health professionals often associate poor adherence to patients' unwillingness to take these medications, it must be emphasized that this problem involves far more issues than patient behaviour. Lack of encouragement, support, trust, follow-up and education, and high costs are only a few possible contributors to the problem of nonadherence in Canada and elsewhere. In our view, this problem has more to do with the health care system and health care professionals than with patients themselves.

CONCLUSIONS

Our data suggest that patients with cardiovascular disease who exhibit adherence to statins after one or two years generally remain adherent over subsequent years. Also, adherence to other medications, such as ACE inhibitors and beta-blockers, is likely related to statin adherence in many patients. In the present population, nonadherence was not unique to or more marked with statin medications; patients were equally likely to neglect ACE inhibitors or beta-blockers.

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DISCLAIMER: This study is based in part on nonidentifiable data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

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Exhibit 1105-2

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Special Report: Interventions to Improve Patient Adherence with Medications for Chronic Cardiovascular Disorders*

TEC

Assessment Program
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Executive Summary

The objective of this Special Report is to review the evidence on the effectiveness of interventions to improve patient adherence with prescribed cardiovascular medications. Due to the large quantity of literature in this area published over an extended period of time, and the existence of numerous published systematic reviews, the approach taken is a "review of reviews." Published systematic reviews that have addressed this specific question will be identified and examined in-depth. The quality of the evidence will be both judged on the methodological quality of the systematic reviews, and also on the quality of the evidence contained in the primary studies.

Interventions will be grouped into several broad categories: simplified dosing schedule; behavioral interventions; educational interventions; and "complex" interventions (those consisting of more than one discrete component). Adherence rates will be the main outcome measure, and rates of adherence for patients receiving the intervention will be compared to rates in patients not receiving the intervention. Interpretation of the evidence will address both whether interventions are effective, as judged by significant group differences between control and intervention, and the magnitude of the improvement that resulted from the intervention.

The final evidence base consists of 7 systematic reviews, which in turn include evidence from 69 primary studies. In 6 of these 7 reviews, the individual studies could be grouped by type of intervention; there were 21 studies using dose simplification, 9 using behavioral interventions, 6 using complex interventions, and no studies that used education alone. Formal quality assessment of the systematic reviews did not reveal major sources of bias in selection of studies or interpretation of evidence.

Despite the large quantity of evidence, only a limited number of conclusions can be made. There is evidence that a variety of interventions can be effective in improving adherence. There is consistent and robust evidence that simplifying medication dosage schedules leads to improved adherence. The greatest improvement in adherence occurs when medications dosed more than twice daily are compared to once-daily dosing. However, given the current preponderance of once- and twice-daily medications in clinical practice, the relevance and potential benefit of this type of intervention is diminished.

For other categories of interventions, the evidence is not adequately robust to conclude that such approaches are efficacious as a group. Some behavioral interventions demonstrate evidence for significant improvements in adherence but others do not. The overall evidence on behavioral

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* Please note: This Special Report is a "review of reviews" concerning evidence on effectiveness of interventions to improve patient adherence with prescribed cardiovascular medications. It does not attempt to address the question as to whether the TEC criteria are met.

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interventions suggests that the benefit of single-strategy interventions is not expected to be large. No evidence was identified that evaluated education alone as a single intervention, although education was included as a component of some complex interventions.

Complex interventions showed benefit in some of the studies, and the magnitude of the benefit was generally larger than reported for single-strategy interventions. However, many of the complex interventions are resource intensive, and may not be easily replicated or implemented in today's environment. This limits the generalizability of the results of trials that employ complex interventions. Furthermore, it is not possible to determine which specific components of these complex strategies resulted in benefit, thus making it difficult to design pragmatic interventions.

Conclusions are limited mainly by the quality of the primary studies themselves. The literature base is incomplete in that many potential types of interventions, e.g., education, have not been adequately tested in high-quality trials. There is a lack of trials that target populations that are expected to benefit most, such as patients who have demonstrated non-adherence. Also, there are no trials that tailor interventions to the specific needs of patients. As a result, it is not possible to determine the expected magnitude of benefit for specific interventions applied to specific populations. Furthermore, there is virtually no evidence available to determine the comparative efficacy of different interventions, or the comparative efficacy of a single intervention applied to different populations.

Contents

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Objective

The objective of this Special Report is to review the evidence on the effectiveness of interventions to improve patient adherence with prescribed cardiovascular medications. Due to the large quantity of literature in this area published over an extended period of time, and the existence of numerous published systematic reviews, the approach taken is a "review of reviews." Published systematic reviews that have addressed this specific question will be identified and examined in-depth. The quality of the evidence will be both judged on the methodological quality of the systematic reviews, and also on the quality of the evidence contained in the primary studies.

Interventions will be grouped into several broad categories: simplified dosing schedule; behavioral interventions; educational interventions; and "complex" interventions (those consisting of more than one discrete component). Adherence rates will be the main outcome measure, and rates of adherence for patients receiving the intervention will be compared to rates in patients not receiving the intervention. Interpretation of the evidence will address both whether interventions are effective, as judged by significant group differences between control and intervention, and the magnitude of the improvement that resulted from the intervention.

Background

Adherence with medical care is a broad, complex topic. Patient adherence with prescribed medications is just one component of overall adherence, but is itself a broad topic that can be conceptualized in different ways. This Special Report takes a disease-specific approach, focusing on chronic cardiovascular disorders. A disease-specific approach to adherence is useful since the issues vary considerably across different diseases and different treatment modalities. For example, in psychiatric disorders, symptoms of the condition itself (e.g., the presence of depressive and/or psychotic symptoms) may play a large role in adherence. In these cases, disease control and medication adherence are intricately related. For certain medical diseases such as diabetes or asthma, adherence involves a large degree of disease self-management. Thus, it is difficult to separate the effects of adherence with self-management activities from the effects of adherence with medication taking, both of which may impact outcomes.

Chronic cardiovascular disorders represent an attractive area of focus since these conditions allow a relatively clean evaluation of adherence with medication use. The majority of disorders in this class, such as hypertension and hyperlipidemia, are asymptomatic conditions for which chronically administered medications have a direct beneficial effect on outcomes. Adherence with cardiovascular medications is therefore less confounded by symptom control and/or other disease management activities.

Non-adherence with prescribed cardiovascular medications is widespread. In hypertension, it is commonly cited that 50% of patients who are prescribed anti-hypertensive medication treatment drop out of treatment (Vermeire et al. 2001). Of patients who persist with treatment, an additional one-third does not take sufficient doses to achieve optimal blood pressure control (Vermeire et al. 2001). Despite these general percentages commonly cited, precise information is lacking on rates of different subtypes of non-adherence, adherence in specific patient populations, or adherence with specific treatment modalities.

The etiology of non-adherence is complex, and potentially fraught with value-laden attributes. Contributing factors may be related to patient behavior and beliefs, provider behavior and beliefs, as well as features of the current health care system itself. These behavioral and other contributing factors can be described, without attempting to impugn the motivations behind the behaviors or the societal policies that create barriers to care. Thus, although this Special Report refers to patient adherence, the patient may or may not have control over many of the factors that contribute to non-adherence.

Defining and Measuring Adherence

The complexity of the issues around patient adherence with medications is reflected in the many different patterns of medication non-adherence that have been described. These are often classified into the broad categories of intentional and unintentional non-adherence. Intentional non-adherence refers to instances where patients consciously decide not to take medications as prescribed. This is most often manifest as a failure to fill a prescription after it is given, or a failure to refill a medication that

the patient had previously started. Patients may decide not to fill a prescription due to beliefs that the medication is not effective, fear of adverse effects, cost, or inconvenience. These decisions may result from a lack of information, poor communication, inadequate access to care, or may be related to emotional factors such as anxiety and/or depression.

Another form of intentional non-adherence is overdosing or underdosing. Patients may take more than the prescribed dose if they feel that "more is better," coupled with a lack of understanding of principles of drug dosing. Conversely, patients may take less than the prescribed dose due to adverse effects or costs, which again may be associated with poor understanding of drug dosing.

Unintentional non-adherence is more common than intentional non-adherence, and refers to situations in which patients attempt to adhere but are not successful. This typically results in underdosing as a result of random or systematic missed doses. A "drug holiday" occurs when a patient stops a medication for a period of time, for example, due to procrastination in obtaining a refill. Another pattern of unintentional non-adherence is called a "chaotic" pattern, in which a patient takes approximately the correct number of doses, but not at the prescribed intervals. A chaotic pattern may result when patients inadvertently miss doses, and then "double-up" or increase their subsequent dose(s) in an attempt to make up for the missed dose(s).

There are similar complexities encountered in measuring adherence. A number of potential methods can be used, but none is ideal. The choice of method will substantially influence the absolute rates of adherence that are reported, and may even influence the ability to detect any improvements in adherence that result from an intervention (Dunbar-Jacobs and Mortimer-Stephens 2001).

Patient self-report is used in clinical practice and has also been used in research studies, but has the greatest potential subjectivity. A less-subjective method is "pill counts," a common approach in research studies. Pill counts are performed by having patients bring in their medication bottle(s). A researcher then counts the number of pills that have been removed from the bottle(s) over a specified period of time. Another less-subjective method is pharmacy records, if available, which represent a direct and objective measure of medication refills, although not necessarily the actual amount of medication taken. Measurement of drug levels in the blood or urine is the most direct and objective method of monitoring, but also the most expensive and least convenient.

Electronic monitors for measuring adherence have been developed recently; these are primarily intended for use in clinical research trials. These monitors fit onto the medication bottles supplied to the patient, and record each time the bottle is opened and pill(s) are removed, thus providing a record of both the number of pills removed and the timing of removal. Many researchers consider electronic monitoring systems to be the current gold standard for measuring adherence in clinical trials (Claxton et. al. 2001; Mallion and Schmitt 2001). Comparisons between patient self-report, pill counts and electronic monitoring demonstrate lower rates of adherence when measured by electronic monitoring compared to other methods. This implies that patient report and pill counts systematically overestimate adherence compared to electronic monitoring (Mallion and Schmitt 2001), and that electronic monitoring is more likely to yield results that are closer to the true adherence rate.

An overriding problem in measuring adherence is the vulnerability of measurements to the "Hawthorne effect," i.e., a change in patient behavior as a result of being monitored in a study. This is especially true when the patient knows the methods being used to measure adherence, or anticipates negative consequences resulting from non-adherence. Even with the more objective methods of measurement, such as pill counts or electronic monitoring, patients can remove medications that have not been taken from the bottle in attempts to appear to be more adherent than they actually are. Blood or urine levels of drug are perhaps the most objective measure, but can still be influenced by patient behavior if they know when the levels will be taken and adhere carefully for several days prior to measurement (the "toothbrush effect"). Novel research designs, such as not informing patients that adherence is being measured, can alleviate this problem, but may be problematic in other ways.

Regardless of the type of measurement used, adherence outcomes can be reported in different ways. Mean adherence rates can be expressed as a continuous variable ranging

from 0–100%, representing the percentage of prescribed medication(s) taken. Another common way of reporting adherence is to dichotomize "adherence" or "non-adherence" by whether a threshold percentage medication is taken (typically greater than 80% of prescribed medication). This allows outcomes to be reported at the patient level, as the percentage of patients that are adherent. However, this threshold for defining adherence is somewhat arbitrary, and has not been validated empirically as a clinically significant cutoff point.

Factors Associated with Non-adherence
Numerous clinical and demographic factors have been associated with medication non-adherence. However, predictors vary across different clinical populations and according to the methods used to measure adherence (Dunbar-Jacob and Mortimer-Stephens 2001). Due to this variability, together with the large number of different predictors identified in various clinical populations, and the inter-relationships among many of these factors, it is not currently possible to accurately predict adherence with medications (Dunbar-Jacob and Mortimer-Stephens 2001).

The complexity of dosing schedule and adverse effects are prominent factors that are consistently associated with adherence (Vermeire et al. 2001). Adherence is inversely correlated with the number of medications prescribed and the frequency of dosing. Adverse effects are frequently cited as the principal reason for discontinuing medications (Balkrishnan 1998). Furthermore, rates of discontinuing prescribed medications correlate with the incidence and severity of adverse effects, especially for asymptomatic conditions (Mallion and Schmitt 2001).

Adherence rates differ for specific medications, even when prescribed for the same clinical condition. Adherence with statins for hyperlipidemia has been shown consistently to be higher than adherence with other classes of lipid-lowering agents such as resins or niacin (Avorn et al. 1998). For hypertension, numerous studies have shown that adherence is higher with angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers, when compared to diuretics or beta-blockers. Differences in adherence rates for particular medications that treat the same disorder are likely related to adverse effects or inconvenience issues (Avorn et al. 1998; Mallion and Schmitt 2001).

Demographic factors associated with adherence include age, race, gender, marital status and socioeconomic status, but these demographic factors tend to be weak predictors of adherence (Vermeire et al. 2001; Dunbar-Jacob and Mortimer-Stephens 2001). Increasing age is positively associated with adherence, although this relationship does not hold for elderly patients (Vermeire 2001). For patients above 65, some studies have reported that adherence is inversely correlated with advancing age while other studies have reported no relationship between age and adherence (Dunbar-Jacob and Mortimer-Stephens 2001; Balkrishnan 1998). Caucasian race is associated with higher adherence rates when compared with African-American and other minorities, as is higher socioeconomic status (Balkrishnan 1998). Single patients have lower adherence rates overall when compared to married patients (Dunbar-Jacob and Mortimer-Stephens 2001).

A variety of social and behavioral factors have been associated with non-adherence, but the predictive ability of these types of factors has been inconsistent (Balkrishnan 1998). Patient beliefs and expectations are related to adherence, but these factors are difficult to measure, categorize and quantitate. Beliefs and concerns about taking medications can have an impact on adherence; these types of factors are highly individualized and intertwined with family, cultural and religious beliefs. Factors related to affect and mood, such as depressive symptoms, have been linked to lower rates of adherence. Similarly, higher level of social support has been shown to correlate with increased adherence.

Finally, costs and access may be important predictors of adherence in certain populations, but not in others. For elderly patients and inner-city urban populations, the cost of medications has been demonstrated to be an important factor in adherence (Balkrishnan 1998), while cost is often not an issue for insured populations. Lower income levels and lower socioeconomic status is associated with lower adherence, although this relationship holds even when full coverage for prescribed medications is available (Avorn et al. 1998).

Some of these factors are modifiable, such as type or dose of medication and can be easily changed without detriment to patients, providers, or society. Other factors are generally not modifiable, such as age, socioeconomic status, or insurance status. Still others, such as deficits

in knowledge or cultural beliefs, may be somewhat modifiable if targeted interventions are devised. However, interventions targeting these types of factors need to respect the autonomy of patients' belief systems and the primacy of patients' authority for medical decision-making.

Effect of Non-adherence on Outcomes

The effect of non-adherence on outcomes of chronic cardiovascular disorders remains incompletely understood. In clinical trials, it has been well established that outcomes are better for patients who adhere to therapy compared with those who do not (McDermott et al. 1997; DiMatteo et al. 2002). DiMatteo et al. (2002) performed a quantitative meta-analysis of the relationship between adherence and outcomes across a wide variety of disorders. The combined relative risk for adverse outcomes in non-adherent patients compared with adherent patients was 3.4 (95% CI: 1.6–7.4) for patients with hypertension, 2.8 (95% CI: 1.7–4.7) for patients with hyperlipidemia, and 1.5 (95% CI: 0.9–2.4) for patients with heart disease.

However, adherent patients may differ from non-adherent patients on a variety of clinical and demographic variables that potentially confound the causal relationship between non-adherence and outcomes. For example, patients with hypertension who are adherent with medications are also more likely to adhere with other beneficial health behaviors such as diet and exercise. While it is likely that non-adherence results in important negative effects on clinical outcomes, the research in this area has not adequately defined the extent to which differences in outcomes are solely attributable to non-adherence.

Insight into this problem can be obtained from clinical trials that compare outcomes of adherent and non-adherent patients in both the experimental and control groups. In 3 large cardiovascular clinical trials that reported these data (Table 1), non-adherent patients in the placebo group had similar elevations in the relative risk for adverse outcomes as did non-adherent patients in the experimental group (McDermott et al. 1997). This has led some authors to speculate that adherence may be a marker for a variety of health behaviors that are linked to improved outcomes. If this is true, then the potential benefits associated with improved adherence may be overestimated, and interventions intended to improve adherence may not achieve the desired effects on health outcomes (McDermott et al. 1997).

Interventions to Improve Adherence

Numerous different interventions intended to improve adherence have been evaluated in clinical trials. These range from single interventions such as dose simplification or automated reminders to complex, multi-modal interventions involving behavioral, educational, and/or affective components. For the purposes of this Special Report, interventions will be classified into the following 4 categories: 1) dosing changes; 2) educational programs; 3) behavioral programs (including counseling and other psychosocial components); and 4) "complex" interventions consisting of multiple individual components. Table 2 gives examples of types of interventions in each category that have been described in the literature (adapted from Roter et al. 1998).

Methods

Search Methods

The MEDLINE database was searched using the Medical Subject Heading® (MeSH®) term "patient adherence" cross-referenced with the terms (all fields): (medication OR drug OR pharmaceutical OR prescription), Limits: Review. The search was performed from January 1980 through October 2003 and was limited to English-language articles reporting

Table 1. Outcomes of Non-Adherent Patients in a Large Cardiovascular Trial (Adapted from McDermott et al. 1997)

Study	Outcome	RR for Outcome in Non-adherent Patients Placebo	Active Drug
Coronary Drug Project Research Group	Mortality at 5 years	1.9	1.6
β-Blocker Heart Attack Trial Research Group	Mortality at 2 years	2.5 (95% CI: 0.9–7.0)	3.1 (95% CI: 0.9–10.3)
Gallagher et al. 1993	Mortality at 2 years	2.8 (95% CI: 1.0–7.6)	1.9 (95% CI: 0.5–6.1)

Table 2. Interventions to Improve Adherence Described in the Literature (adapted from Roter et al. 1998)

Dosing Change	Educational Interventions	Behavioral Interventions	"Complex" Interventions
Less frequent dosing Transdermal dosing Adherence-enhancing packaging	Individual – Oral – Audiovisual – Written – Telephone – Mail – Home visits Group – Peer group – Family – Inpatient	Monitoring and feedback Skill-building Contracting Tailoring schedule Memory aids Diaries Calendar Overt pill count Rewards Reminders – Mailed – Telephone – Computerized Home visits Family support and counseling	Combination of 2 or more of interventions from previous categories

on human subjects. Initial search was supplemented with the "related articles" function for several key articles. Computerized searches were supplemented by manual reviews of bibliographies of selected references, pertinent Cochrane reviews, and review of *Current Contents*. A total of 565 citations were initially identified. The titles and abstracts of all these citations were reviewed for potential relevance as a systematic review. A total of 59 potential systematic reviews were identified, retrieved, and reviewed in-depth against the article inclusion-exclusion criteria.

Study Selection

Studies were selected for inclusion in this Special Report if they met the following criteria:

1. Full-length articles published in peer-reviewed journals in the English language between 1980 and 2003
2. Article was a systematic review, defined as reporting explicit criteria for:
   a. Comprehensive literature search
   b. Article selection
3. Review focused on patients with cardiovascular disorders OR reported separately on studies of patients with cardiovascular disorders
4. Review focused on interventions to improve adherence OR reported separate results for interventions intended to improve adherence in patients with cardiovascular disorders

Quality Assessment for Systematic Reviews

The quality of each systematic review was assessed by a method adapted from West et al. (2002). These authors identified 11 domains of a systematic review that could be reviewed for quality, and suggested essential elements for each that should be present in a high-quality systematic review. These are shown in Table 3.

Medical Advisory Panel Review

This Special Report was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on October 15, 2003. In order to maintain the timeliness of the scientific information in this Special Report, literature search updates were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, and did not change the results of the Special Report, the results of these studies were included in the tables and text where appropriate.

Problem Formulation

Patient Indications

Patients who are prescribed medications for a cardiovascular disorder comprise the intended population. Cardiovascular disorders are defined to include both actual cardiac conditions such as angina pectoris and conditions

Table 3. Domains of Quality Assessment in Systematic Reviews (West et al. 2002)

Domain	Essential Elements	Empirical Basis
Study Question	Question clearly specified and appropriate	No
Search Strategy	Sufficiently comprehensive and rigorous, with attention to possible publication biases	Yes
Inclusion/Exclusion Criteria	Selection methods specified and appropriate, with a priori criteria specified if possible	No
Interventions	Intervention(s) clearly detailed for all study groups	No
Outcomes	All potentially important harms and benefits considered	No
Data Extraction[1]	Rigor and consistency of process Number and types of reviewers Blinding of reviewers Measurement of agreement or reproducibility Extraction of clearly defined interventions/exposures and outcomes for all relevant subjects and subgroups	No
Study Quality/Validity	Assessment method specified and appropriate	Yes
Data Synthesis/ Analysis	Appropriate use of qualitative and/or quantitative synthesis, with consideration of the robustness of results and heterogeneity issues	Yes
Results	Narrative summary and/or quantitative summary statistic and measure of precision, as appropriate	No
Discussion	Conclusions supported by results with possible biases and limitations taken into consideration	No
Funding/Sponsorship	Type and sources of support	Yes

1 A majority of elements must be present for a Yes rating

predisposing to cardiovascular disease such as hypertension and hyperlipidemia.

The specific population of highest interest is patients prescribed medications for cardiovascular disorders who have demonstrated non-adherence. However, since no studies targeted non-adherent patients in this manner, this degree of specificity was not required. The available studies primarily include the general population of patients who are prescribed cardiovascular medications.

Technologies to Be Compared
Interventions aimed at improving adherence will be compared to no intervention, i.e., to usual care.

Health Outcomes
The main outcome of concern will be the adherence rates pre- and post-intervention. The most rigorous way to analyze these rates is to compare the change in adherence between the intervention and control groups. However, most studies do not report change values, but compare post-intervention rates of adherence between groups. Improvements in adherence rates will be used when possible, otherwise post-intervention adherence rates will be examined.

Specific Research Question
What interventions have been shown to be effective in improving adherence with chronic cardiovascular medications?

Review of Evidence

Literature search initially identified 9 systematic reviews that met the inclusion criteria. Two publications presented the same data (McDonald et al. 2002; Haynes et al. 2005) in different formats and were counted as 1 study; another study (Haynes et al. 1976) was superseded by a later publication (McDonald et al. 2002) that repeated the same protocol at a later time. Thus, the evidence reviewed for this Special Report consists of 7 distinct systematic

reviews (Tables 4 and 5). These systematic reviews summarize a total of 69 primary studies, each of which evaluates 1 or more interventions intended to improve adherence (see Appendix). Of these 69 primary studies, most (61/69) are included in only 1 of the systematic reviews. Seven studies are included as part of 2 of the systematic reviews, and 1 study is included in 3 systematic reviews.

The reviews differ substantially in scope and in the number of primary studies included. Some are narrowly focused, with clinical question(s) that look at one aspect of adherence (e.g., Iskedjian et al. [2002], "...to compare rates of adherence with once-daily, twice-daily, and more than twice-daily dosing.") or one particular type of intervention (e.g., Bennett and Glasziou [2003], focusing on trials of computer-generated medication reminders). Other reviews are broader in scope, with less-focused objectives (e.g., Newell et al. [1999] "...to critically review the literature regarding interventions to improve cardiovascular patients adherence with medication taking"; or Roter et al. [1998] "...summarize the results of studies that evaluated the effectiveness of interventions to improve patient adherence with medical regimens"). The number of primary studies included ranges from 4 to 34, with the 2 largest reviews (Claxton et al. 2001, n=25; Roter et al. 1998, n=32) accounting for approximately three-quarters of the primary studies (57/78).

Another area of variability is in the inclusion criteria used to select primary studies into these systematic reviews. Some systematic reviews had lenient inclusion criteria, thereby increasing the likelihood that studies in that category would be included. Other studies used stricter inclusion criteria, incorporating direct or indirect measures of quality into their inclusion criteria. Four of the reviews were confined to randomized controlled trials (Bennett and Glasziou 2003; Peterson et al. 2003; McDonald et al. 2002; Newell et al. 1999), and some of these required further quality criteria such as an "unconfounded" trial (McDonald et al. 2002), a minimum number of subjects (Peterson et al. 2003), or a minimum quality score (Newell et al. 1999).

In reviewing the evidence for this Special Report, each systematic review will first be critiqued as to its methodologic quality. Particular concern will be given to whether any methodologic factors limit the validity of the article selection and/or interpretation of evidence. Next, the evidence on effectiveness of interventions will be examined by grouping interventions by category, i.e., interventions to simplify dosing schedule, behavioral interventions, educational interventions, and "complex" interventions. Using this approach, data from 6 of the 7 systematic reviews could be classified by intervention type, with one exception (Roter et al. 1998). Roter et al. (1998) reported combined measures of effect size for interventions that included patients with hypertension, cardiovascular disorders, and lipid disorders. However, the interventions were not divided by type and could only be analyzed as a group.

Quality Assessment

The overall quality of these systematic reviews was evaluated by an adaptation of the methods in West et al. (2002; Table 6). Of the 11 quality indicators, the systematic reviews met between 6 and 11. One study (Iskedjian et al. 2002) met all quality indicators; this was a meta-analysis of adherence by different dosing schedules. Another study met 10 of 11 indicators (McDonald et al. 2002), failing only on the lack of a focused research question. Most of the reviews did not demonstrate a focused question, with only the 2 meta-analyses of dosing regimens meeting this criterion. Certain other criteria, i.e., search strategy, clear description of interventions, clear reporting of results, and reporting of funding/sponsorship were met by all studies. Other criteria were met by some studies and not others, e.g., well-formed inclusion and exclusion criteria were found in 4/7 studies; adequate description of data extraction in 4/7; and evaluation of study quality in 4/7.

Quality review did not suggest that bias was likely to have affected the selection of articles and/or the interpretation of evidence. All reviews demonstrated a comprehensive search strategy and article inclusion criteria that could be applied explicitly. All reviews presented the results clearly and there was only 1 (Bennett and Glasziou 2003) in which the discussion and conclusions did not appear to be supported by the actual evidence. Therefore, the quality of the systematic reviews is adequate to form valid conclusions about the overall body of evidence. The overall quality of this body of evidence is more dependent on the quality of the individual studies included in the reviews than on the quality of the systematic reviews themselves.

Table 4. Study Formulation for Included Articles

Study/Yr	Formulation of Question	Patient Population(s) (relevant for this review)	Intervention(s) (relevant for this review)	Outcome(s)
Bennett and Glasziou 2003	"To systematically review randomized controlled trials of computer-generated medication reminders..."	All patients prescribed medication in included studies	Any system that used computers to assist in identifying patients and generating reminders	Rates of adherence
Peterson et al. 2003	"To examine the results of meta-analyses addressing the net effect of tools and methods to enhance drug adherence in patients with hyperlipidemia."	Patients prescribed lipid-lowering agents for hyperlipidemia	Any intervention intended to improve adherence with lipid-lowering medications	Effect size – estimated absolute difference in adherence rates between groups by binomial effect size display
Iskedjian et al. 2002	"...to compare rates of adherence with once daily, twice daily, and greater than twice daily dosing."	Adults (>18 years of age) prescribed medications for essential hypertension.	Less frequent dosing (Comparison of different dosing schedules)	Rates of adherence Effect size – difference in adherence rates between two dosing schedules
McDonald et al. 2002	"...systematically review published RCT's of interventions to assist patients' adherence to prescribed medications."	All patients prescribed medications for: - HTN - hyperlipidemia	Any intervention to assist patients in adhering to medications.	One or more measures of both adherence and clinical treatment outcome
Claxton et al. 2001	"...to determine the associations between dose frequency and medication adherence."	All patients prescribed medication in included studies	Less frequent dosing (Comparison of different dosing schedules)	Rates of adherence
Newell et al. 1999	"...critically review the literature regarding interventions to improve CV patients' adherence with medication-taking...."	Patients with CV disease or with increased risk factors for CV disease.	Any intervention to assist: - Medication-taking - Obtaining refills	Effectiveness of intervention(s)
Roter et al. 1998	"...summarize the results of studies that evaluated the effectiveness of interventions to improve patient adherence with medical regimens."	All patients prescribed medications for: - HTN - CV disorders - hyperlipidemia	Any intervention that was a systematic attempt to influence or improve adherence with therapeutic recommendations.	Combined effect size – reported as the correlation between intervention and adherence outcome.

Abbreviations Key: See Appendix

Table 5. Study Methodology for Included Articles

Study/Yr	Literature Search	Inclusion/Exclusion Criteria	Data Extraction	Quality Assessment	Data Synthesis	Reporting of Results	Funding/ Sponsor
Bennett and Glasziou 2003	Electronic search of multiple databases, 1966-2001. Hand search of relevant bibliographies.	1) Randomized controlled trial; 2) Intervention that used computers to assist in identifying patients and generating reminders	Dual review of potentially relevant articles Data abstraction by 2 reviewers	Quality instrument developed for RCTs, possible total score 17	Qualitative synthesis	Tabular and narrative summary	None reported
Peterson et al. 2003	Electronic search of multiple databases, 1966-2000.	1) Interventions for patients; 2) Randomized controlled trial; 3) At least 10 pts in each group	Abstraction by 1 of "three external reviewers trained to abstract data"	none	Quantitative synthesis of effect size by random effects model and binomial effects size display	Tabular and narrative summary	Rx industry
Iskedjian et al. 2002	Electronic search of multiple databases, English & French. Manual search of articles/textbooks	1) Comparative study reporting adherence for two or more dosing schedules; 2) Medications prescribed for ≥10 weeks; 3) Quality score at least 50% (8.5/17) of total.	Screen of abstracts by 1 reviewer. Dual review of relevant articles, dual data abstraction	Quality checklist consisting of 6 domains, total possible score of 17	Quantitative synthesis of effect size by random effects model. Analysis of heterogeneity	Tabular summary	"No external funding"
McDonald et al. 2002	Electronic search of multiple databases. Hand search of bibliographies. Expert review.	1) Unconfounded RCT; 2) Intervention to improve adherence; 3) At least 6 mos. f/u; 4) At least 80% f/u in each group; 5) Reported adherence & treatment outcome.	Dual review of abstracts, potentially relevant articles. Data abstraction by 2 reviewers	Modified Jadad scale	Qualitative synthesis Quantitative analysis considered but rejected due to disparate nature of included studies	Narrative summary	Gov't (Canada)
Claxton et al. 2001	Electronic search of multiple databases, 1986-2000. Hand search of relevant bibliographies.	1) Studies that reported dosing and medication adherence rates; 2) Used an electronic monitor to evaluate dose and adherence	NR	none	Reported mean, SD, and range of adherence rates averaged across included studies	Tabular summary	Rx industry

Abbreviations Key: See Appendix

Table 5. Study Methodology for Included Articles (cont'd)

Study/Yr	Literature Search	Inclusion/Exclusion Criteria	Data Extraction	Quality Assessment	Data Synthesis	Reporting of Results	Funding/ Sponsor
Newell et al. 1999	Electronic search of multiple databases 1985-1996. Hand search of biblio-graphies. Expert review	1) Pts with CV disease or risk for CV disease; 2) Intervention aimed at increasing adherence with medications; 3) Randomly allocated pts to treatment; 4) Good or Fair quality (score of at least 18/35)	Data extraction by one author. Dual extraction on 20% sample of studies.	Quality instrument developed for RCTs, possible total score 35	Qualitative synthesis	Tabular summary	National Heart Foundation (Australia)
Roter et al. 1998	Electronic search of multiple databases, 1977-1994. Hand search of relevant bibliographies.	1) Control group; 2) Adherence measured quantitatively; 3) Association between adherence and intervention reported or able to calculate; 4) Sample size ≥10	NR	none	Reported effect size as correlation (Pearson's r) between intervention and adherence outcome.	Combined analysis of various subgroups.	National Pharmaceutical Council

Abbreviations Key: See Appendix

Table 6. Quality Assessment of Included Systematic Reviews

Study/Yr	Study Question	Search Strategy	Inclusion/ Exclusion	Interventions	Outcomes	Data Extraction	Study Quality	Data Synthesis	Results	Discussion	Funding
Bennett and Glasziou 2003	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No
Peterson et al. 2003	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Iskedjian et al. 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McDonald et al. 2002	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Claxton et al. 2001	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Newell et al. 1999	No	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes
Roter et al. 1998	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes

Abbreviations Key: See Appendix

Interventions Using Simplified Dosing Regimens

Simplification of dosing was the most commonly studied of all intervention types. It was addressed in 5 of the 7 systematic reviews, and was the exclusive focus of 2 systematic reviews (Iskedjian et al. 2002; Claxton et al. 2001). In 4 of the reviews, analysis focused on the efficacy of less-frequent dosing, while the fifth review analyzed adherence with a weekly transdermal patch versus a daily oral medication (Table 7).

In all cases, there was a significant improvement in adherence associated with less frequent dosing. For the comparison of once-daily (QD) versus twice-daily (BID) dosing, the difference in mean adherence between control and intervention ranged from 6–11%. Larger differences were reported for the comparisons of once-daily versus greater than twice-daily dosing (8–28%) and twice-daily dosing versus greater than twice-daily dosing (0–18%). Therefore, the greatest benefit is achieved in changing from a regimen that is greater than twice-daily dosing to a regimen that is once-daily dosing.

The potential benefit of these interventions depends on current medication prescribing patterns, particularly whether chronic medications prescribed 3 or 4 times daily can be easily switched to a comparable medication taken once daily. Recent trends in manufacturing and prescribing have resulted in the majority of cardiovascular prescribed as once-daily or twice-daily formulations. Medications taken more than twice daily are much less commonly prescribed currently in clinical practice.

Furthermore, the relevance of some dose simplification strategies tested in the literature may be diminished as new agents become available. For example, statin drugs are currently the overwhelmingly preferred agent(s) for treatment of hyperlipidemia. In the systematic review by Peterson et al. (2003) that focused on patients with hyperlipidemia, 3 of the 4 studies addressed medications other than statins, and did not compare outcomes to those of statins.

Interventions Using Educational Methods

No studies were included that tested education alone as a single intervention to improve adherence. Education was included with some behavioral interventions, for example home nurse visits (Johnson et al. 1978) and was included as 1 component of some of the complex interventions.

Interventions Using Behavioral Methods

Four systematic reviews addressed the category of behavioral interventions, and these 4 reviews included 9 primary studies that used a single behavioral intervention intended to improve adherence (Table 8). Although there is a wide range of possible behavioral interventions (see Table 2), the available literature addresses only a relatively narrow spectrum of these. In 6 of these 9 studies, the intervention was a reminder system. Other behavioral interventions included were improving the convenience of care (worksite care and home visits), special packaging, and self-monitoring. Many potential types of behavioral interventions were not addressed by any of the evidence in this review.

The majority of the comparisons in these studies did not show statistically significant group differences (Table 8). The intervention groups had higher adherence rates than the control groups in nearly all cases, but the differences reached statistical significance in only 1 study (Skaer et al. 1993a). A second study showed small, nonsignificant absolute differences in adherence rates between the control and intervention group; these differences achieved statistical significance when analyzed in a multivariate model controlling for covariates (Table 8).

"Complex" Interventions Using Multiple Modalities

"Complex" interventions are defined as programs that consist of more than 1 discrete component, for example an education component combined with a behavioral component such as a medication diary. These types of programs are often interdisciplinary in nature. Each component may have an independent effect on adherence and there may be interactions between individual components of the program that effect outcomes.

Two systematic reviews addressed this category of intervention, and reviewed a total of 6 primary studies (Table 9). In 3 studies, Burelle (1986), Haynes et al. (1976), and Logan et al. (1979), there were significant differences in adherence rates post-intervention, with relatively large differences in mean adherence between the intervention and control groups of 19%, 21%, and 23%, respectively.

The 3 additional studies (Miller et al. 1988; Miller et al. 1989; Miller et al. 1990) did not show any significant group differences. These

Table 7. Results: Studies Evaluating Simplified Dosing Regimens

Review/Yr	Study	n (studies)/ n (patients)	Comparison	Adherence Rates: Once-daily	Twice-daily	> Twice daily	p value
Peterson et al. 2003	Brown 1997	1/31	BID vs. QID		96%*	85%**	<0.001* NS**
Iskedjian et al. 2002	Combined	5/2,152	QD vs. BID	93% ± 2.3%	87% ± 2.9%		<0.03
	Combined	7/4,669	QD vs. >BID	91% ± 2.2%		83% ± 3.5%%	<0.001
	Combined	4/8,926	BID vs. >BID		91% ± 4.7%	91% ± 2.2%	
McDonald et al. 2002	Baird 1984a	1/389	QD vs. BID[1]	96%	90%		0.06
			QD vs. BID[2]	93%	82%		0.009
	Girvin 1999	1/54	QD vs. BID		96%*	85%**	<0.001*
	Brown 1997	1/62	BID vs. QID				NS**
Claxton et al. 2001	Combined		QD vs. BID	79% ± 14%	69% ± 15%		NS
	Combined		QD vs. TID	79% ± 14%		65% ± 16% (TID)	0.003
	Combined		QD vs. QID	79% ± 14%		51% ± 20% (QID)	<0.001
	Combined		BID vs. TID		69% ± 15%	65% ± 16% (TID)	NS
	Combined		BID vs. QID		69% ± 15%	51% ± 20% (QID)	0.001
Newell et al. 1999	Burris 1991	1/58	Qwk (transdermal) vs. QD	Transdermal 96%	Once-daily 50%		<0.01

Abbreviations Key: See Appendix

* p-value for change from baseline value
** p-value for change from baseline value

1 Adherence defined as percentage of patients taking more than 80% of prescribed doses
2 Adherence defined as percentage of patients taking more than 90% of prescribed doses

Table 8. Results: Studies Evaluating Behavioral Interventions

Review/Yr	Study	n (studies)/ n (patients)	Intervention Group(s)	Control Group	Adherence Rates: Group	Pre-	Post-[1]	p value[2]
Peterson 2003	Schectman 1994	1/162	Telephone reminders weekly by trained healthcare professional for first month of drug therapy	Usual care	Control		NS	
					Intervention			
Bennett 2003	Baird 1984b	1/324	Mailed reminders for refills to patients	Usual care	Control	NR	20%	
					Intervention	NR	18%	NR
	Simkins 1986	1/207	1. Mailed reminders 2. Telephone reminders	Usual care	Control	NR	58%	
					Intervention 1	NR	65%	NR
					Intervention 2	NR	42%	
	Raynor 1993	1/197	Medication timetable given to patients on hospital discharge	Usual care	Control	NR	62%	
					Intervention	NR	87%	NR
Newell 1999	Skaer 1993b	1/304	1. Mailed reminders 2. Special packaging 3. Reminders + packaging	Usual care	Control	NR	56 ± 7	
					Intervention 1	NR	64 ± 8	<0.05
					Intervention 2	NR	67 ± 6	<0.05
					Intervention 3	NR	79 ± 9	<0.05

1 Reported as mean adherence rate for entire group, unless otherwise indicated
2 p-value for intervention group vs. control group, unless otherwise indicated
3 Reported as percentage of patients who are adherent, defined as taking at least 80% of prescribed medication

Table 8. Results: Studies Evaluating Behavioral Interventions (cont'd)

Review/Yr	Study	n (studies)/ n (patients)	Intervention Group(s)	Control Group	Adherence Rates: Group	Pre-	Post-[1]	p value[2]
McDonald 2002	Sackett 1975	1/134	1. Worksite care	Usual care	Control	NR	48%[3]	NS
			2. Education		Intervention 1	NR	62%[3]	NS
			3. Worksite + education		Intervention 2	NR	53%[3]	NS
					Intervention 3	NR	48%[3]	NS
	Johnson 1978	1/136	1. Self-monitoring	Neither intervention	Control	70 ± 6	69 ± 7	NS
			2. Home visits		Intervention 1	68 ± 6	78 ± 5	NS
			3. Monitoring + visits		Intervention 2	65 ± 6	68 ± 8	NS
					Intervention 3	66 ± 5	76 ± 5	NS
	Becker 1986	1/171	Special packaging with reminders	Usual packaging	Control	NR	84%[3]	
					Intervention	NR	75%[3]	NS
	Friedman 1996	1/301	Telephone-linked computer reminder	Usual care	Control	94.0%	93.6%	
					Intervention	93.0%	95.4%	NS
					Δ adherence (adjusted for covariates)			
					Control	17.7%		
					Intervention	11.7%		0.03

1 Reported as mean adherence rate for entire group, unless otherwise indicated
2 p-value for intervention group vs. control group, unless otherwise indicated
3 Reported as percentage of patients who are adherent, defined as taking at least 80% of prescribed medication

[redacted]

Table 9. Results: Studies Evaluating "Complex" Interventions

Review/Yr	Study	n (studies)/ n (patients)	Intervention Components	Control Group	Adherence Rates: Group	Pre-[1]	Post-[1]	p value[2]
Newell et al. 1999	Burelle 1986	1/16	Home visits; education; medication planner; dose packaging; referrals to other support agencies	Usual care	Control	NR	71% ± 12	
					Intervention	NR	92% ± 4.6	<0.001
	Miller 1988	1/103	Nurse visit at 1 month and 2 months: problem identification, coping methods, health planning	Usual care	Control	NR	18.2 ± 2.8[3]	
					Intervention	NR	17.8 ± 2.2[3]	NS
	Miller 1989	1/81	Nurse visit at 1 month; adherence assessment; counseling; written health plan	Usual care	Control	NR	18.6 ± 2.4[3]	
					Intervention	NR	18.8 ± 2.3[3]	NS
	Miller 1990	1/64	Nurse visit at 1 month; adherence assessment; counseling; written health plan	Usual care	Control	NR	19.2 ± 3.0[3]	
					Intervention	NR	18.7 ± 3.7[3]	NS
McDonald et al. 2002	Haynes 1976	1/38	Tailored medication schedule; self-monitoring; rewards	Usual care	Control	45% ± 7.1	43% ± 10	
					Intervention	45% ± 5.6	66% ± 8.2	0.03
	Logan 1979	1/457	Worksite nurses; tailored medication schedule; self-monitoring; rewards	Usual care at MD office	Control	NR	49.1%	
					Intervention	NR	67.6%	<0.005

1 Reported as mean adherence rate for entire group, unless otherwise indicated
2 p-value for intervention group vs. control group, unless otherwise indicated
3 Score on medication adherence scale, range of possible scores 0-20

studies were performed in different populations, but were done by the same research team, using very similar designs. In addition, these authors did not report adherence rates. Their main outcome measure was an adherence scale with a range of 0–20. This scale may have had reduced sensitivity to detect changes due to a ceiling effect, in that all scores are in the range of 16–20.

This evidence suggests that complex interventions may lead to greater improvements in adherence compared with single-strategy interventions. However, since the programs are multimodal but analyzed as a single intervention, it is not possible to determine which component(s) of these programs results in improved adherence. Also, the evidence is limited by the narrow range of modalities that have been tested in clinical trials. The generalizability of the available evidence from one complex program to another is limited, and the reported results can only be considered valid for the specific program studied and the specific population enrolled. Difficulties in replication and implementation of these types of multimodal interventions are a barrier to translating these results to clinical practice.

Interventions of Mixed Types

Roter et al. (1998) reviewed a total of 153 studies of interventions to improve adherence for numerous clinical conditions. Included in the larger review were 24 studies of patients with hypertension, 7 studies of patients with cardiovascular disorders, and 2 studies of patients with hyperlipidemia. The authors calculated a combined effect strength (ES) for studies of hypertension, cardiovascular disorders, and hyperlipidemia, but did not further subclassify interventions by type. The effect sizes for each of the diagnostic categories were mostly in the small to moderate range, and were largest for studies of hypertension. However, the effect strength also varied widely by the method used to measure adherence, especially within the studies of hypertension (Table 10). Studies of hypertension that used an indirect measure of adherence, largely pill counts, reported an effect size in the "large" range (0.76), whereas the effect size was in the 'small' range for studies that used a direct measure such as blood levels (0.23) or a subjective measure such as patient self-report (0.15).

Since this review did not separate interventions by type, no conclusions can be drawn regarding the efficacy of different types of interventions. The combined analysis does corroborate data from other reviews in demonstrating that interventions can have a beneficial effect on adherence. Also, this review highlights the importance of considering the type of measurement used when evaluating adherence outcomes, and demonstrates how the type of measurement can affect conclusions drawn from the evidence.

Limitations of the Evidence

The current review attempts to evaluate the efficacy of interventions to improve patient adherence with cardiovascular medications, covering a large quantity of literature published over a long period of time. In reviewing this body of evidence, the "review of reviews" approach allows greater efficiency in identifying and interpreting evidence from primary studies. However, a limitation of this approach is the potential for selection bias when considering the body of primary studies that are included in the final review. These studies were selected for inclusion by the authors for their own systematic review, according to criteria that may not exactly match the intended characteristics for this review. Inclusion criteria for each systemic review may have been more or less strict, depending on the intent of the researchers. More strict inclusion criteria may reduce the likelihood that any study in that category will be included in the final body of evidence.

Despite the large volume of literature, there are major gaps in the evidence base on medication adherence. More accurate information is needed on the frequency of different types of non-adherence, adherence rates across different diseases and with different classes of medications. A more complete understanding of the interplay between the many factors associated with adherence could improve the ability to predict and identify non-adherent patients. This type of information would allow researchers to target improvement efforts where the benefit is expected to be greatest.

The literature base is incomplete in that only a relatively narrow spectrum of interventions have been evaluated compared with the large number of potential different programs that can be devised. The available clinical trials evaluating interventions do not reflect the complexity of the clinical issues. The current theoretical understanding of adherence allows

Table 10. Results: Reviews Combining All Interventions, Regardless of Intervention Type

Study/Yr	Condition	n (studies)/ n (patients)	Type of Adherence Measure (number of studies)		Adherence Rates[1] ES	Adherence Rates[1] p-value
Roter et al. 1998	Hypertension	24/?	Direct[2]	(n=8)	0.23	<0.0001
			Indirect[3]	(n=6)	0.76	<0.0001
			Subjective[4]	(n=11)	0.15	<0.0001
	Cardiovascular	7/?	Direct[2]		—	—
			Indirect[3]	(n=4)	0.02	NS
			Subjective[4]	(n=3)	0.30	<0.05
	Lipids	2/?	Direct[2]		—	—
			Indirect[3]		—	—
			Subjective[4]	(n=4)	0.13	<0.0001

1 Reported as combined effect strength by binomial effect-size display (BESD)
2 Tracer substances and/or physiologic indicators of adherence in blood or urine
3 Pill counts, prescription refills, or use of mechanical or electronic monitor(s)
4 Patient's or others' reports of adherence, or review of medical charts

classification of non-adherence into numerous distinct categories, with different health behaviors expected to be associated with each. However, most trials take a "one size fits all" approach to designing and testing interventions. They do not target patients with demonstrated non-adherence, nor do they tailor interventions toward specific behaviors or types of non-adherence that are most prevalent. As a result, the effect of any particular intervention is diluted by the inclusion of substantial numbers of patients who are either adherent to start with, or who would not be expected to respond to the particular intervention studied.

Summary and Conclusions

There is a large quantity of literature on adherence and many published trials that evaluate interventions intended to improve adherence. The literature includes numerous systematic reviews that evaluate the efficacy of interventions to improve adherence. This Special Report examined these systematic reviews in depth to determine whether the evidence is sufficient to form conclusions on the efficacy of interventions to improve adherence. Interventions were classified into 4 broad categories: dose simplification, educational, behavioral, and complex interventions.

The final evidence base consists of 7 systematic reviews, which in turn include evidence from 69 primary studies. In 6 of these 7 reviews, the individual studies could be grouped by type of intervention; there were 21 studies using dose simplification, 9 using behavioral interventions, 6 using complex interventions, and no studies that used education alone. Formal quality assessment of the systematic reviews did not reveal major sources of bias in selection of studies or interpretation of evidence.

Despite the large quantity of evidence, only a limited number of conclusions can be made. There is evidence that a variety of interventions can be effective in improving adherence. There is consistent and robust evidence that simplifying medication dosage schedules leads to improved adherence. The greatest improvement in adherence occurs when medications dosed more than twice daily are compared to once-daily dosing. However, given the current preponderance of once- and twice-daily medications in clinical practice, the relevance and potential benefit of this type of intervention is diminished.

For other categories of interventions, the evidence is not adequately robust to conclude that such approaches are efficacious as a group. Some behavioral interventions demonstrate evidence for significant improvements in adherence but others do not. The overall evidence on behavioral interventions suggests that the benefit of single-strategy interventions is not expected to be large. No evidence was identified that evaluated education alone as a single intervention, although education was included as a component of some complex interventions.

Complex interventions showed benefit in some of the studies, and the magnitude of the benefit was generally larger than reported for single-strategy interventions. However, many of the complex interventions are resource intensive, and may not be easily replicated or implemented in today's environment. This limits the generalizability of the results of trials that employ complex interventions. Furthermore, it is not possible to determine which specific components of these complex strategies resulted in benefit, thus making it difficult to design pragmatic interventions.

Conclusions are limited mainly by the quality of the primary studies themselves. The literature base is incomplete in that many potential types of interventions, e.g., education, have not been adequately tested in high-quality trials. There is a lack of trials that target populations that are expected to benefit most, such as patients who have demonstrated non-adherence. Also, there are no trials that tailor interventions to the specific needs of patients. As a result, it is not possible to determine the expected magnitude of benefit for specific interventions applied to specific populations. Furthermore, there is virtually no evidence available to determine the comparative efficacy of different interventions, or the comparative efficacy of a single intervention applied to different populations.

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Appendix

Table A. Primary Studies Included in Systematic Reviews

Primary Study	Systematic Review: Bennett	Peterson	Iskedjian	McDonald	Claxton	Newell	Roter
Baird 1984a			X	X			X
Baird 1984b	X						
Becker 1986				X			X
Berger 1991							X
Binstock 1988							X
Bloemberg 1991							X
Boissel 1996			X				
Brown 1997		X		X			
Brun 1994					X		
Burrelle 1986						X	
Burnier 1999					X		
Burris 1991						X	X
Carney 1995					X		
Detry 1995			X		X		
Dickinson 1981							X
Eisen 1990			X				
Farmer 1994			X				
Friedman 1996				X			
Fujii 1986			X				
Girvin 1999				X			
Gonzalez-Fernandez 1990							X
Guerrero 1993					X		
Halpern 1993			X				
Haynes 1976				X			
Hilleman 1993			X				
Johnson 1978				X			
Kelly 1988							X
Kirscht 1981							X
Kluger 1983							X
Kruse 1992					X		
Kruse 1993					X		

Table A. Primary Studies Included in Systematic Reviews (cont'd)

Primary Study	Systematic Review						
	Bennett	Peterson	Iskedjian	McDonald	Claxton	Newell	Roter
Kruse 1994					X		
Lee 1996					X		
Leenon 1997					X		
Levine 1979							X
Levy 1979							X
Logan 1979				X			X
Lueg 1991					X		
Maiman 1992							X
Mallion 1992					X		
Mallion 1995					X		
Mallion 1996					X		
Mallion 1998					X		
McDowell 1989							X
Mengden 1993					X		
Miller 1988						X	X
Miller 1989						X	
Miller 1990						X	X
Morisky 1980							X
Morisky 1982							X
Morisky 1985							X
Morisky 1990							X
Mounier-Vehier 1998					X		
Muhlhauser 1993							X
Nessman 1980							X
Nikolaus 1991							X
Raynor 1993	X						
Rudd 1990					X		
Rudd 1991					X		
Rudd 1993					X		
Sackett 1976				X			
Schectman 1994		X					
Sclar 1991							X
Sclar 1992							X
Simkins 1986	X						
Skaer 1993a						X	
Skaer 1993b							X

Table A. Primary Studies Included in Systematic Reviews (cont'd)

	Systematic Review						
Primary Study	Bonnett	Peterson	Iskedjian	McDonald	Claxton	Nowell	Rotor
Straka 1997					X		
Swain 1981							X
Taggart 1981							X
Takala 1979							X
Tanner 1981							X
Vander Stichele 1992					X		
Waeber 1984					X		
Wallen 1994					X		
Webb 1980							X
Weidler 1992					X		
Wirebaugh 1993							X

Key to Abbreviations in Tables

Δ	change
BESD	binomial effect-size display
BID	twice daily
CI	confidence interval
CV	cardiovascular
ES	effect strength
HTN	hypertension
MD	doctor
N	number
NR	not reported
NS	not significant
pt(s)	patient(s)
QD	once daily
QID	four times daily
Qwk	once weekly
RCT(s)	randomized, controlled trial(s)
RR	relative risk
Rx	drug; pharmaceutical
SD	standard deviation
TID	three times daily
Yr	year

Exhibit 1105-3

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ORIGINAL REPORT

Use and adherence to beta-blockers for secondary prevention of myocardial infarction: who is not getting the treatment?†

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SUMMARY

Purpose To characterise those who receive beta-blocker therapy after MI and to estimate the effect of adherence to beta-blocker use on subsequent mortality and recurrent MI.

Methods A community-based observational cohort study was done using a record linkage database. Patients were those discharged from hospitals after their first MI between January 1994 and December 1995 and who also survived for at least 1 year. The outcome was all cause mortality and recurrent MI. Results were adjusted for age, sex, social deprivation, airways disease, peripheral vascular disease (PVD), diabetes mellitus, cardiovascular drug use, steroid use and hospitalisation for cardiovascular disease using a logistic regression model and a Cox regression model.

Results A total of 865 patients were included in this study. 386 (44.6%) were on beta-blocker treatment during the year after MI. Beta-blocker use was lower amongst high-risk patients (older patients, patients with obstructive airway disease, PVD and those with a previous hospitalisation for heart failure). Mortality was lower in patients treated with beta-blockers compared with those untreated. Good adherence (≥80%) was associated with a lower adjusted relative risk of mortality compared with unexposed patients (0.49, 95%CI 0.30–0.80, $p < 0.01$). Within the high-risk subgroup of patients, the adjusted relative risk of mortality with good adherence was 0.40 (0.17–0.93, $p = 0.03$).

Conclusions Beta-blocker use was lower in older patients, patients with airways disease, PVD and heart failure, but these patients appeared to have the greatest benefit from beta-blockers. Good adherence to beta-blocker treatment after MI was associated with a lower risk of mortality.

KEY WORDS — beta-blockers; post-MI; adherence; mortality

INTRODUCTION

Randomised clinical trials have convincingly shown clinically important benefits of beta-blockers for the secondary prevention of myocardial infarction (MI).[1–4] However, several studies such as EUROASPIRE[5] have shown that many subjects are not given beta-blockers following MI. In the past, physicians have prescribed beta-blockers for fewer than one third of their patients, and cardiologists for less than a half of their patients with MI.[6] One possibility is that subjects with airways disease are not given these agents for fear of worsening their condition. Another is that subjects with peripheral vascular disease (PVD) are denied these as beta-blockers are said to worsen this condition. Thirdly, patients with heart failure may not get a beta-blocker even though they are unquestionably beneficial in this condition. Finally, diabetic patients do not get these drugs prescribed as

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beta-blockers are alleged to mask the symptoms of hypoglycaemia despite the fact that most diabetic subjects have type II diabetes, the treatment for which rarely induces hypoglycaemia. All of these high-risk subjects have higher mortality than subjects without these conditions.

The therapeutic effect of a drug depends not only on patients having the treatment prescribed but also on their adherence or compliance with the treatment. Non-adherence or poor adherence to drug treatment is a significant problem in the management of chronic disease and interventions to improve adherence are complex, labour-intensive and not predictably effective.[7] Reports on the underuse of beta-blockers in MI patients have focussed on patients at discharge and few studies have addressed drug use post-discharge. The aims of this study were to characterise those subjects who receive beta-blocker therapy following MI and to estimate the effect of adherence to beta-blocker use on subsequent mortality and recurrent MI.

METHODS

The study was carried out in the population of the Tayside region in Scotland, using the MEMO record-linkage database. The data collection methods for this database have previously been described.[8] In brief, this database contains several data sets including all dispensed community prescriptions, hospital discharge data, biochemistry data and other data that are linked by a unique patient identifier, the community health index number. These data are made anonymous for the purposes of research as approved by the Tayside Caldicott Guardians. The project was also approved by the Tayside committee on research medical ethics.

Study population

Subjects resident in Tayside and registered with a general practitioner between January 1989 and December 1999, formed the study population. These subjects were residents of Tayside throughout the study period or died during the study period.

Study subjects

All subjects who were hospitalised for their first MI from 1 January 1994 until 31 December 1995 and who survived for 1 year formed the study cohort. Follow-up data were collected on each subject until December 1999. The minimum follow-up for each subject was 4 years.

Drug utilisation

Each dispensed beta-blocker prescription has details of the date of prescription, daily dose, amount and duration. Adherence to beta-blockers use was calculated as the number of days with beta-blocker supply divided by the total number of days from the first prescription for a beta-blocker to the end of the year following discharge from the hospital for each patient.

Definition of myocardial infarction

Diagnosis of MI was ascertained from the hospital discharge diagnosis data (SMR1) coded by primary ICD9 code and ICD10 code.

Outcome variables

The outcomes of the study were beta-blocker use in the year after MI and mortality or recurrent MI during the follow-up period. Recurrent MI was defined as hospitalisation with a diagnosis of MI or sudden cardiac death.

Statistical analysis

Data were summarised as mean (SD) for continuous variables and number of subjects (%) for categorical variables. χ^2 and t-tests were performed to determine significant differences. The logistic regression model was used to analyse those receiving beta-blockers following MI and the proportional hazards model was used to analyse the time to death or recurrent MI, giving results in term of risk or hazard ratios. To minimise confounding by indication, where beta-blockers might be selectively given to patients because of their underlying condition, a propensity score[9] was calculated and then was adjusted for in the final proportional hazards model. The propensity score is the conditional probability of exposure to a treatment given observed covariates. To determine the propensity score, a logistic regression model was constructed in which the dependent variable was the treatment group and the independent variables were predictors of treatment. Covariates in the final model included demographic details, prior obstructive airway disease (OAD), cardiovascular disease, diabetes mellitus, PVD, prior beta-blocker use, use of calcium blockers, angiotensin-converting enzyme inhibitors, alpha-blockers, antihypertensive drugs, thiazide diuretic, loop diuretic, nitrates, antiplatelet drugs, lipid-lowering prescriptions and steroid prescriptions. All statistical analyses were carried out using

SAS version 8 (SAS Institute, Cary, North Carolina, U.S.A.).

RESULTS

There were 865 patients aged 30–93 years old (mean age 66.3, SD 12.2) in this study. Of these, 386 (44.6%) took beta-blocker treatment during the year after discharge from their first MI. About 90% of patients (349 out of 386) started on beta-blocker treatment within 3 months after their discharge and 40 patients stopped the treatment after their first prescription (mean duration 43 days, SD 16.9). A total of 198 (22.9%) patients died and 197 (22.8%) patients experienced at least one further MI during a median of 3.7-years of follow-up. About 88% of beta-blocker use was atenolol at a mean dose of 48 mg/day (SD 18.5). Table 1 shows beta-blocker use and adherence to beta-blocker treatment in post-MI patients in the year after discharge from hospital. Older patients, patients with OAD, PVD, diabetes and heart failure were less likely to be on beta-blocker treatment. A test for trend also showed that there was a significant difference in age between the beta-blocker use group and the non-use group. Overall, 58.5% patients ($n = 226$) had greater than or equal to 80% (226/386) adherence to beta-blocker treatment. Adherence to beta-blocker treatment was poorer in older people (trend test $p = 0.0214$) and in female patients χ^2 test, $p = 0.0006$). Patients with OAD disease or with previous beta-blocker use tended to have better adherence. After adjustment for known covariates, patients with OAD and heart failure were significantly less likely to receive beta-blocker treatment (Table 2). Patients with previously prescribed beta-blockers were almost three times more likely to receive beta-blocker treatment than patients not previously prescribed beta-blockers.

Table 3 shows the results of multivariate Cox regression analysis for all-cause mortality and recurrent MI. After adjustment for demographic and other covariates, patients with greater than or equal to 80% adherence to beta-blocker treatment were significantly associated with a lower risk of all-cause mortality. A linear trend test for hazard ratio (HR) of all-cause mortality was also significant ($p = 0.0169$). Among high-risk group of patients (patients with OAD or heart failure or diabetes or PVD, $n = 291$), men had a higher all cause mortality (adjusted HR 1.89, 95%CI 1.17–3.05, $p = 0.0091$) but there was no increased risk of recurrent MI (0.99, 0.60–1.63 $p = 0.9590$). Multivariate analysis showed that good adherence to beta-blocker treatment was significantly associated with a lower risk of all-cause mortality (HR 0.40, $p = 0.0343$)

Table 1. Characteristics of patients who received or did not receive beta-blocker treatment during the first year after their first MI

Characteristic	Number of patients	Yes n (%) ≥80% Adherence	Yes n (%) <80% Adherence	No n (%)	p value*
Total	865	226 (26.1)	160 (18.5)	479 (55.4)	
Age (years)†					
<50	89	42 (47.2)	21 (23.6)	26 (29.2)	<0.001
50–59	152	56 (36.8)	39 (25.7)	57 (37.5)	
60–69	262	79 (30.1)	50 (19.1)	133 (50.8)	
70–79	241	45 (18.7)	39 (16.2)	157 (65.1)	
≥80	121	4 (3.3)	11 (9.1)	106 (87.6)	
Sex					
Male	514	164 (31.9)	89 (17.3)	261 (50.8)	<0.001
Female	351	62 (17.7)	71 (20.2)	218 (62.1)	
Deprivation category					
1–2 Least deprived	178	48 (27.0)	25 (14.0)	105 (59.0)	0.502
3–4	352	90 (25.6)	72 (20.4)	190 (54.0)	
5–7 Most deprived	323	84 (26.0)	62 (19.2)	177 (54.8)	
Previous disease history					
OAD	131	18 (13.7)	7 (5.3)	106 (80.9)	<0.001
Heart failure	96	9 (9.4)	10 (10.4)	77 (80.2)	<0.001
Diabetes mellitus	74	15 (20.3)	15 (20.3)	44 (59.4)	0.486
PVD	53	8 (15.1)	8 (15.1)	37 (69.8)	0.078
Previous year beta-blocker use	159	66 (41.5)	33 (20.8)	60 (37.7)	<0.001

OAD, obstructive airway disease; CHF, congestive heart failure; PVD, peripheral vascular disease.
*Comparison of all three columns.
†Trend test between age groups, $p = 0.0214$.

Table 2. Results of odds ratios for receiving beta-blockers following MI

	Unadjusted		Adjusted*	
	OR	95%CI	OR	95%CI
Age (+1 year)	0.94	0.93–0.95	0.94	0.92–0.95
Sex (m vs. f)	1.59	1.21–2.10	0.98	0.70–1.37
Prior beta-blocker use	2.41	1.69–3.43	2.82	1.83–4.36
Previous disease history				
OAD	0.24	0.15–0.39	0.30	0.15–0.60
Diabetes mellitus	0.83	0.51–1.35	0.93	0.57–1.65
CHF	0.27	0.16–0.46	0.33	0.19–0.60
PVD	0.52	0.28–0.94	0.64	0.31–1.32

OAD, obstructive pulmonary disease; CHF, congestive heart failure; PVD, peripheral vascular disease.
*Adjusted for age, sex, social deprivation, prior OAD, cardiovascular disease, diabetes mellitus, PVD, prior beta-blocker use, prior use of calcium blockers, angiotensin-converting enzyme inhibitors, alpha-blockers, antihypertensive drugs, thiazide diuretic, loop diuretic, nitrates, antiplatelet drugs, lipid-lowering and steroid prescriptions.

(Table 4). However, there was no significant reduction in risk of recurrent of MI.

DISCUSSION

Beta-blockers were given to less than half the patients discharged with an MI in the present study and this is similar to the finding of other studies.[4,5,10,11] The Cooperative Cardiovascular Project evaluated the relationship between beta-blocker treatment and outcome in more than 200 000 patients hospitalised for MI. The study showed that only 34% of patients were prescribed beta-blockers at the time of discharge from the hospital.[4] The EUROASPIRE I and II group[5] reported that overall beta-blocker use increased from 53.7% (range 34.7–77.8%) to 66.4% (47.3–87.9%) between the first survey (1995–1996) and the second survey (1999–2000) across the nine European countries. Wide variations of prescribing patterns between regions and hospitals were found in Australia, Canada and U.S.A.[11,12] In general, women were less likely to be prescribed beta-blockers as was found in our study and elsewhere.[13]

Table 3. Adjusted hazard ratios in post-MI patients

	All-cause mortality		MI recurrence	
	HR	95%CI	HR	95%CI
Adherence to beta-blockers (%)				
0 ($n=479$)	1.00		1.00	
<80 ($n=160$)	0.83	0.53–1.29	0.50	0.31–0.81
80–100 ($n=226$)	0.49	0.30–0.80	0.69	0.46–1.03
Age (+1 year)	1.07	1.05–1.10	1.02	1.00–1.05
Sex (m vs. f)	1.49	1.09–2.03	1.40	1.03–1.92

Adjusted for propensity score, age, sex, social deprivation, prior OAD, cardiovascular disease, diabetes mellitus, PVD, prior beta-blocker use, prior use of calcium blockers, angiotensin-converting enzyme inhibitors, alpha-blockers, antihypertensive drugs, thiazide diuretic, loop diuretic, nitrates, antiplatelet drugs, lipid-lowering drugs and steroid prescriptions.

Table 4. Adjusted hazard ratios in high risk group of post-MI patients

	All-cause mortality		MI recurrence	
	HR	95%CI	HR	95%CI
Adherence to beta-blockers (%)				
0 ($n=216$)	1.00		1.00	
<80 ($n=31$)	0.71	0.33–1.53	0.98	0.46–2.09
80–100 ($n=44$)	0.40	0.17–0.93	0.97	0.45–2.09
Age (+1 year)	1.07	1.04–1.10	1.03	1.00–1.06
Sex (m vs. f)	1.89	1.17–3.05	0.99	0.60–1.63

Adjusted for propensity score, age, sex, social deprivation, prior OAD, cardiovascular disease, diabetes mellitus, PVD, prior beta-blocker use, prior use of calcium blockers, angiotensin-converting enzyme inhibitors, alpha-blockers, antihypertensive drugs, thiazide diuretic, loop diuretic, nitrates, antiplatelet drugs, lipid-lowering drugs and steroid prescriptions.

The percentage of patients on treatment was low in the OAD group (19.1%), heart failure group (19.8%) and patients ≥80 years old group (12.4%). This is consistent with other studies findings.[4,14–17] However, beta-blocker therapy was associated with a 40% reduction in mortality, a benefit that extended across a variety of high-risk group patients.[4,18–21]

The benefits of beta-blocker treatment for the secondary prevention of MI have been well documented. However, there are little data on adherence to beta-blocker treatment post-MI. Adherence to drug treatment outside of clinical trials is poor. Adherence to beta-blocker treatment in the present study was slightly lower than adherence to statin therapy[22] (63.7% adherence to statin treatment in post-MI patients). Butler's study[23] showed that about 61% of patients still collected their beta-blocker prescriptions 1 year following their MI. But in Mitra's study,[24] of 156 AMI patients discharged from a government University-affiliated teaching hospital on beta-blocker treatment 71% patients were still on beta-blocker treatment after 2 years follow-up. The difference in adherence to beta-blocker treatment between different studies may be explained by different population characteristics, prescribing habits or health care systems or different measurements of adherence. Our adherence to beta-blocker treatment was calculated as the number of days

of beta-blocker supply divided by the total number of days from the first prescription for a beta-blocker to the end of year after discharge from the hospital whilst in others studies adherence was measured as filling the prescription at the time of follow-up. These previous studies did not count the duration of each prescription and this may have resulted in an overestimate or underestimate of adherence. Many factors such as patient education, attitude toward taking medication, fear of adverse effects, difficulty in managing more than one dose a day, older age, psychological state and the relationship with the physician can affect patient's adherence. Older patients tended to have poorer adherence to beta-blocker treatment as has been shown elsewhere.[22,23] In our study 40 patients in the poor adherence group discontinued their medication after their first prescription. These were mainly older, socially deprived females.

Our study has several limitations. We assumed that if a prescription was encashed then patients would take treatment but we had no way of knowing whether patients actually swallowed the pills. However, this problem is not unique and in fact applies to the vast majority of studies including randomised controlled trials. Our adherence index was calculated in the year after discharge from the hospital. Prescribing data beyond the year after discharge was not studied. Adherence patterns may have changed in some patients but this is expected to be small as Bulter's study[23] showed that adherence to beta-blockers was only slightly lower at 1 year compared with 6 months. Our study also showed that only 10% (40 out of 386) of patients stopped their treatment after their first prescription. However, some people may have started the beta-blocker treatment after 1995 but this is probably a small effect as 95% of patients started their treatment within 6 months after their discharge.

We did not have information on smoking, obesity, exercise and diet, all of which are important risk factors in patients with heart disease. However, we did use the Carstairs socio-economic deprivation score as a surrogate to adjust for atleast some of these factors.[26–28] A strength of this study is the population-based cohort design, with complete follow-up over the study period. This approach allows a 'real-world' population to be studied representing all socio-economic groups and within a universal healthcare coverage scheme.[29]

In conclusion, beta-blocker use was lower in older patients, patients with previous airways disease, PVD and heart failure, but these patients appeared to have the greatest benefit from beta-blockers. Good adherence to beta-blocker treatment after MI was associated with a lower risk of mortality.

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Exhibit 1105-4

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Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis

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Primary care

Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis

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Abstract

Objective To determine the effect of combinations of statins, aspirin, β blockers, and angiotensin converting enzyme inhibitors in the secondary prevention of all cause mortality in patients with ischaemic heart disease.

Design Open prospective cohort study with nested case-control analysis.

Setting 1.18 million patients registered with 89 general practices across 23 strategic health authority areas within the United Kingdom. Practices had longitudinal data for a minimum of eight years and were contributing to QRESEARCH, a new database.

Patients All patients with a first diagnosis of ischaemic heart disease between January 1996 and December 2003. Cases were patients with ischaemic heart disease who died. Controls were patients with ischaemic heart disease who were matched for age, sex, and year of diagnosis and were alive at the time their matched case died.

Main outcome measures Odds ratio with 95% confidence interval for risk of death in cases compared with controls. Exposure was current use of different combinations of statins, aspirin, β blockers, and angiotensin converting enzyme inhibitors before death in cases, or the equivalent date in controls.

Results 13 029 patients had a first diagnosis of ischaemic heart disease (incidence rate 338 per 100 000 person years), 2266 cases were matched to 9064 controls. Drug combinations associated with the greatest reduction in all cause mortality were statins, aspirin, and β blockers (83% reduction, 95% confidence interval 77% to 88%); statins, aspirin, β blockers, and angiotensin converting enzyme inhibitors (75% reduction, 65% to 82%); and statins, aspirin, and angiotensin converting enzyme inhibitors (71% reduction, 59% to 79%). Treatments associated with the smallest reduction in all cause mortality were β blockers alone (19% reduction, 37% reduction to 4% increase), angiotensin converting enzyme inhibitors alone (20% reduction, 1% to 35%), and combined statins and angiotensin converting enzyme inhibitors (31% reduction, 57% reduction to 12% increase).

Conclusions Combinations of statins, aspirin, and β blockers improve survival in high risk patients with cardiovascular disease, although the addition of an angiotensin converting enzyme inhibitor conferred no additional benefit despite the analysis being adjusted for congestive cardiac failure.

Editorial by Fahey et al

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Introduction

Randomised controlled trials have shown that statins improve the survival of patients with ischaemic heart disease.[1-3] Although combinations of drugs (as proposed in the Polypill)[4] have been received with enthusiasm, we found no direct evidence evaluating the effects of statins, aspirin, β blockers, and angiotensin converting enzyme inhibitors in combination.

Uncritical acceptance of medical innovations or lack of evidence can result in the endorsement of ineffective or potentially dangerous treatments, subsequently leading to the withdrawal of drugs (for example, rofecoxib) or limitations on use.[5-9] Limitations on use can occur years after worldwide adoption, as was the case with hormone replacement therapy.[10] Although randomised trials provide relatively unbiased evidence of the effectiveness of interventions in selected patients, the application of trial results to representative populations of patients is often inaccurate.[11] In addition, further trials can be difficult, or even unethical if a true benefit is suspected.

Routinely collected data from aggregated general practice databases have been used successfully to evaluate the risks and benefits of treatments in a population.[12 13] This method enables access to longitudinal data, to a large sample size, and to representative populations. Also, because data on exposure can be collected before the outcome occurs, recall bias is limited; the quality of the electronic record now surpasses that of the paper based system.[14]

We determined the effect of combinations of drugs in the secondary prevention of all cause mortality in patients with ischaemic heart disease in a large UK population based sample.

Methods

We carried out a prospective open cohort study with nested case-control analysis using data from 89 general practices contributing to a new UK database, QRESEARCH (version 1, downloaded 17 December

2003). This database will ultimately contain the records of over 7.5 million patients from 500 practices in the United Kingdom. For our study we selected only practices with at least eight years of longitudinal data—that is, with Egton Medical Information Services (EMIS) software before 1 January 1996. The practices were spread throughout 23 of the 29 strategic health authority areas across the United Kingdom.

Participants

We identified all patients registered with the practices from 1 January 1996 until the end of the study period (17 December 2003, the date of the most recent computer download at the time of the analysis). Our start date was the 1 January 1996 as this was just over 12 months after the publication of the Scandinavian simvastatin survival study.[1] Our open cohort was selected on the basis of registration dates and dates of leaving the study or death. We identified all patients with incident ischaemic heart disease diagnosed after the 1 January 1996 from the date of first diagnosis of the disease recorded on computer. To minimise information bias, we excluded patients whose diagnosis was made within the first three months of registration with the general practice, patients prescribed statins before the diagnosis of ischaemic heart disease, and patients with a first diagnosis after death (postmortem diagnosis).

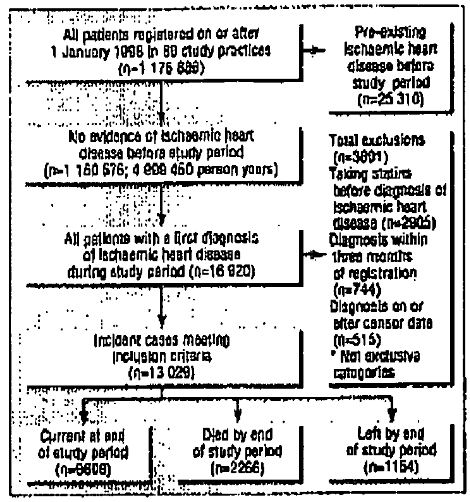
Nested case-control study

We undertook a nested case-control analysis to determine the effects of different combinations of drugs on survival in patients with ischaemic heart disease. Cases were patients with ischaemic heart disease who died from all causes during the follow-up period, the index date being defined as the date of death. We used incidence density sampling to randomly select four controls for each case, matched for age at diagnosis of ischaemic heart disease (five year bands, <45; 45-49, etc), year of diagnosis, and sex. Controls had to be alive when their matched case died. The index date for controls was the date when their matched case died.

Statistical analysis

For cases and controls we reviewed the medical history and data on exposure between the date of diagnosis of ischaemic heart disease and the index date. To measure exposure for each drug we determined the dates of the first and the last prescriptions before the index date. We considered patients as currently receiving a drug if their last prescription was issued within 90 days before the index date. We derived a categorical variable for exposure, which contained levels according to different combinations of four drugs (statins, angiotensin converting enzyme inhibitors, β blockers, and aspirin) taken within 90 days of the index date. The reference group was no current use of any of these drugs.

We used conditional logistic regression for individually matched case-control studies to derive odds ratios with 95% confidence intervals for the risk of death associated with different combinations of aspirin, angiotensin converting enzyme inhibitors, β blockers, and statins before death, or the equivalent date in the matched controls. We adjusted for comorbidity (diabetes, congestive cardiac failure, hypertension, myocardial infarction) and current use of calcium channel blockers. We also adjusted for last



Flow of patients through trial

recorded smoking status (ever smoker, never smoker, not recorded), body mass index (kg/m²; <25, 25-30, >30, not recorded), and fifth of Townsend score (as a measure of deprivation). The Townsend score was calculated on the basis of the 2001 census data associated with the output area of the patient's postcode. We tested for an interaction between current use of each drug and each type of comorbidity, sex, and age. To address concerns about confounding by indication, we carried out an analysis restricted to patients without diabetes, congestive cardiac failure, or myocardial infarction.[18] All the analyses were carried out in Stata (version 8.2). We selected a P value of 0.01 (two tailed) as statistically significant.

Results

Eighty nine practices met our selection criteria (figure). Overall, 1 175 886 patients were registered on or after 1 January 1996 (604 781 women and 571 105 men), accumulating almost five million (4 999 450 patients) person years of observation. Of these registered patients, 25 310 patients had ischaemic heart disease recorded before 1 January 1996 and were not included in this analysis.

In total, 16 920 patients were identified with a first diagnosis of ischaemic heart disease during the study period (overall incidence rate of ischaemic heart disease 338.4 per 100 000 person years, 95% confidence interval 333.4 to 343.6). The crude incidence of ischaemic heart disease in women was 286.2 per 100 000 person years and in men was 392.4 per 100 000 person years. The age standardised incidence rate per 100 000 person years was, respectively, 250.8, 245.0 to 256.6 and 427.5, 418.9 to 436.1. Our inclusion criteria were met by 13 029 of the 16 920 patients with ischaemic heart disease. During the 43 460 person years of observation there were 2266 deaths for all causes for patients with ischaemic heart disease giving an overall all cause mortality of 52.1 per 1000 person years, 50.9 to 54.3.

Case-control analysis

For the 2266 cases who died during the follow-up period, we identified 9064 controls matched by age, sex, and year of diagnosis who were alive at the time their case died. Cases and controls were well matched at baseline for age and sex (table 1). The median duration of ischaemic heart disease before the index date was 20.3 months for cases and 21.0 months for controls. Overall, 445 cases (19.6% of 2266) had been prescribed any statin compared with 2303 of the controls (25.4% of 9064) between the date of diagnosis of ischaemic heart disease and the index date. Cases had a higher prevalence of congestive cardiac failure, diabetes, and myocardial infarction and a lower prevalence of hypertension (table 1).

Table 2 shows the unadjusted and adjusted odds ratios for the different drug combinations. After adjustment for comorbidity (diabetes, hypertension, congestive cardiac failure, and myocardial infarction), use of calcium channel blockers, smoking status, body mass index (obese, not obese, not recorded), and Townsend score (fifths), the drugs associated with the greatest reductions in odds for all cause mortality were statins, aspirin, and β blockers (83% reduction, 95% confidence interval 77% to 88% reduction); statins, aspirin, angiotensin converting enzyme inhibitors, and β blockers (75% reduction, 65% to 82% reduction); and statins, angiotensin converting enzyme inhibitors, and aspirin (71% reduction, 59% to 79% reduction).

The drugs associated with the smallest reductions in all cause mortality were β blockers alone (19% reduction, 37% reduction to 4% increase), angiotensin converting enzyme inhibitors alone (20% reduction, 1% to 35% reduction), and combined statins and angiotensin converting enzyme inhibitors (31% reduction, 57% reduction to 12% increase).

We found a significant interaction between current use of aspirin and myocardial infarction. In drug combinations containing aspirin, the reductions in all cause mortality were greater in people with myocardial infarction—for example, a combination of statins, aspirin, and β blockers was associated with a 90% reduction in all cause mortality (95% confidence interval 82% to 94%). We found a significant interaction between current use of angiotensin converting enzyme inhibitors and age: drug combinations containing angiotensin converting enzyme inhibitors were associated with greater reductions in all cause mortality in people aged 75 and over. No other significant interactions were found.

Cases had a higher prevalence of congestive cardiac failure, diabetes, and myocardial infarction and a lower prevalence of hypertension. An analysis

Table 1 Characteristics of cases with ischaemic heart disease who died and controls. Values are numbers (percentages) unless stated otherwise

Characteristic	Cases (n=2266)	Controls (n=9064)
Median (interquartile range) age at index date	80 (73-86)	80 (73-85)
Median (interquartile range) No of months between diagnosis and index date	20.3 (6.3-40.5)	20.8 (7.0-40.9)
Women	1003 (44.3)	4012 (44.3)
Men	1263 (55.7)	5052 (55.7)
Median (interquartile range) Townsend score*	-0.8 (-2.7-2.3)	-1.2 (-3.0-1.8)
Drugs used before index date after diagnosis of ischaemic heart disease:		
Any statin	445 (19.6)	2303 (25.4)
Angiotensin converting enzyme inhibitors	1126 (49.7)	3601 (39.7)
Aspirin	1604 (74.8)	6843 (75.5)
β blockers	998 (44.0)	4749 (52.4)
Calcium channel blockers	909 (42.0)	3848 (42.5)
Comorbidity before index date:		
Diabetes	367 (16.2)	1024 (11.3)
Hypertension	840 (37.1)	3699 (40.8)
Congestive cardiac failure	718 (31.6)	1408 (15.5)
Myocardial infarction	802 (39.4)	2531 (27.9)

Four controls per case were matched on age, sex, and year of diagnosis of ischaemic heart disease.
*Townsend score is a proxy measure for material deprivation.

Table 2 Unadjusted and adjusted odds ratios for all cause mortality according to current* use of different combinations of aspirin, statins, β blockers, and angiotensin converting enzyme inhibitors. Values are numbers (percentages) unless stated otherwise

Current use of stated drugs*	Cases (n=2266)	Controls (n=9064)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio† (95% CI)
None	677 (29.9)	1730 (19.2)	1.00	1.00
Statins alone	26 (1.1)	117 (1.3)	0.46 (0.31 to 0.74)	0.53 (0.33 to 0.86)
Angiotensin converting enzyme inhibitors	211 (9.3)	474 (5.2)	1.14 (0.94 to 1.37)	0.80 (0.65 to 0.99)
Aspirin alone	420 (18.5)	1830 (20.2)	0.58 (0.51 to 0.67)	0.58 (0.50 to 0.68)
β blockers alone	109 (4.0)	440 (4.6)	0.63 (0.50 to 0.79)	0.81 (0.63 to 1.04)
Statins or angiotensin converting enzyme inhibitors	35 (1.5)	65 (0.7)	1.14 (0.74 to 1.75)	0.69 (0.43 to 1.12)
Statins and aspirin	72 (3.2)	424 (4.7)	0.37 (0.28 to 0.48)	0.39 (0.29 to 0.52)
Statins and β blockers	20 (0.9)	92 (1.0)	0.48 (0.20 to 0.79)	0.46 (0.26 to 0.82)
Angiotensin converting enzyme inhibitors and aspirin	256 (11.3)	852 (9.4)	0.76 (0.64 to 0.90)	0.54 (0.45 to 0.66)
Angiotensin converting enzyme inhibitors and β blockers	46 (2.0)	144 (1.6)	0.75 (0.53 to 1.00)	0.64 (0.43 to 0.94)
Aspirin and β blockers	151 (6.7)	1087 (12.0)	0.33 (0.27 to 0.41)	0.30 (0.31 to 0.47)
Statins, angiotensin converting enzyme inhibitors, and aspirin	60 (2.6)	310 (3.5)	0.41 (0.31 to 0.56)	0.29 (0.21 to 0.41)
Statins, angiotensin converting enzyme inhibitors, and β blockers	11 (0.5)	34 (0.4)	0.68 (0.34 to 1.37)	0.67 (0.30 to 1.51)
Statins, aspirin, and β blockers	45 (2.0)	622 (6.9)	0.16 (0.11 to 0.22)	0.17 (0.12 to 0.23)
Angiotensin converting enzyme inhibitors, aspirin, and β blockers	71 (3.1)	420 (4.6)	0.41 (0.31 to 0.54)	0.34 (0.26 to 0.45)
Statins, angiotensin converting enzyme inhibitors, aspirin, and β blockers	57 (2.5)	408 (4.5)	0.31 (0.23 to 0.42)	0.25 (0.18 to 0.35)

*Last prescription for drug within 90 days before index date.
†Adjusted for comorbidity (diabetes, hypertension, congestive cardiac failure, and myocardial infarction), use of calcium channel blockers, smoking status, body mass index (obese, not obese, not recorded), and Townsend score (fifths).

restricted to patients without diabetes, myocardial infarction, or congestive cardiac failure showed little change in the odds ratios except for angiotensin converting enzyme inhibitors alone (adjusted odds ratio 1.13, 0.69 to 1.84). Results were similar in an analysis of people aged 65 and over. An analysis restricted to people with recorded smoking status and body mass index gave results with lower odds ratios but wider confidence intervals.

Discussion

Combinations of statins, aspirin, and β blockers improve the survival of high risk patients with ischaemic heart disease, although the addition of an angiotensin converting enzyme inhibitor conferred no additional benefit despite adjustment for congestive cardiac failure. The lack of additional benefit from an angiotensin converting enzyme inhibitor is consistent with the recently reported PEACE trial.[16] Our study is the first large scale, long term community based study to report the effect of different combinations of drugs in the secondary prevention of all cause mortality in patients with ischaemic heart disease. We included patients with multiple comorbidity, elderly people, and women who may have been excluded from previous clinical trials.

The QRESEARCH database was validated by comparing the age-sex structure of the population with the 2001 census, the birth and death rates with figures from the Office for National Statistics, the prescribing rates with prescribing analysis and cost (PACT) data, the consultation rates with data from the general household survey, and prevalence data for common conditions with published data and data from similar databases such as the General Practice Research Database. We found good correspondence for all of these measures (data not shown). We also compared practices taking part in regional research networks on these and other measures and found good correspondence.[17] Detailed analyses have shown high levels of completeness and consistency.[18] We also carried out an analysis on these data to compare the effect of statins on overall all cause mortality with that reported in the Scandinavian simvastatin survival study[1] and found a similar reduction in unselected patients in the community over an eight year period.[19]

Our study was observational and therefore at risk of bias and confounding. For example, confounding by indication could have occurred if patients with a better prognosis were more likely to be prescribed different combinations of treatments. This is a particular concern with observational studies of intended drug effects.[12] If residual confounding explained our results then we would have expected the adjusted odds ratios from the restricted analysis to tend towards one, which was not the case in general. As mortality was high in this cohort, caution is needed in interpreting the odds ratios as relative risks. The measure of deprivation we used was calculated at an area level and there will be some heterogeneity within areas, which may result in some residual confounding.

Our identification of patients for the cohort was based on a diagnostic code for ischaemic heart disease rather than a definition that would have allowed the inclusion of patients prescribed cardiac drugs. Our study was designed in this way as our main exposures were drugs.

Our outcome (whether patients died or not) is likely to be well recorded on the general practice clinical database. In the United Kingdom, a national electronic procedure comes into operation when a patient dies. This automatically updates the patient's electronic health record with the date of death. As our study comprised a nested case-control analysis and data were recorded prospectively, recall bias was not possible as the exposure data were recorded on computer before the date of death or the equivalent date in controls.

Misclassification of exposure status is unlikely as more than 99% of all repeat prescriptions from general practice are recorded on computer, and currently these drugs are not available over the counter. The exception is aspirin, and some patients taking this might have been misclassified on practice databases. This is likely to be a small proportion as patients over 65 are entitled to free prescriptions in the United Kingdom and so tend to have these prescribed rather than buy them. Such misclassification, if present and if non-differential, would have had the effect of biasing the odds ratio towards one, making the exposure seem less protective or less harmful.[20] Simvastatin is now also available over the counter, but this will not have affected our results as it was given over the counter status in 2004, after our study had ended.

By excluding patients with a diagnosis of ischaemic heart disease within the first three months of registration with their practice, we reduced possible information bias from pre-existing diseases being recorded as if they were new events at registration.

Although we adjusted for several confounders, residual confounding may have resulted from misclassification of those variables and confounding by unmeasured variables. Such effects would have to be large to account for the substantial protective effects reported here.

We have not investigated the effect of the combination treatments in patients without ischaemic heart disease. Our results should therefore not be taken as evidence that the combination of treatments suggested by Wald et al should be prescribed to all patients over 55.[7]

What is already known on this topic

Statins are associated with improved survival in patients with ischaemic heart disease

Direct evidence is lacking for the effects of combinations of drugs in cardiovascular disease

What this study adds

Combinations of statins, aspirin, and β blockers improve survival in high risk patients with cardiovascular disease

The addition of an angiotensin converting enzyme inhibitor conferred no additional benefit

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Contributors: JHC initiated and designed the study, obtained ethical approval, undertook the data extraction and manipulation and some of the analyses, and drafted the paper. She will act as guarantor for the paper. CC contributed to the study design and core ideas, undertook some of the analyses, advised on interpretation, and contributed to drafting the paper.

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The bad news and the bad news

I recently saw a 64 year old man with a skin lesion on his knee that had been intermittently weeping pus over the past four weeks and had been growing in size. The lesion was well demarcated, granulomatous, and about 2×2 cm in size. He had had it for over a year, but it had never bothered him until recently. The lesion did not look infected, so I decided to remove it and send it for histology.

Four days later, I was called by a consultant pathologist, who started quizzing me about this patient. Specifically he wanted to know the patient's sexual orientation and whether he was an intravenous drug user. The patient was homosexual, and when I told the consultant so it seemed to confirm his suspicion. "This looks like a nodular Kaposi's sarcoma," he said, "but I will need to send it to an expert in London to confirm this as I am really not certain."

From what I knew about Kaposi's sarcoma, it was nearly always linked to HIV infection. I felt apprehensive about telling the patient of the diagnosis for several reasons: I still had no definite confirmation that this was Kaposi's sarcoma (the London expert would have the final word on that) and I would have to tell the patient he had a cancer and very possibly HIV infection as well. Talk about breaking bad news. I therefore decided not to tell the patient until I had the expert opinion.

I finally heard back from the consultant in London: "Yes this has all the features of Kaposi's sarcoma." I called the patient in and broke the bad news to him. I told him that there was a good chance that this form of cancer was linked with being HIV positive, and he understood this. He explained that he had always avoided the issue of HIV testing because he was frightened. He was understandably shaken.

In our surgery we put alerts on the patient's computer records and had a "critical event" meeting to alert all staff about the "high risk patient." I talked to the regional genito-urinary medicine clinic, where the patient was seen then next day.

Then, a week later, I received some unexpected news from the clinic (the patient having given consent for the information to be sent to me): several HIV tests had been carried out, and all were negative. Everyone was most surprised. The patient had no Mediterranean or Jewish background and did not seem to be immunocompromised, so why had he developed the sarcoma? The patient telephoned me and was understandably over the moon. From thinking that he was HIV positive to having "just" a skin cancer made a huge difference to him.

This incident made me think of how rarely things are clear cut in medicine. All the surgery staff were convinced that this patient was infected with HIV, possibly even immunocompromised with AIDS. It turned out we were all wrong. As doctors, we rely on odds and likelihood, but it is important to bear in mind that sometimes the unlikely (odd) will happen and take us by surprise.

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